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TUBERCULOUS MENINGITIS*

Combined Therapy with Cortisone and Antimicrobial Agents

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SYDNEY, NOVA SCOTIA

THREE factors contribute to the unsatisfactory results that have been obtained in the treatment of tuberculous meningitis during the streptomycin era: mechanical obstruction of the circulatory channels of the cerebrospinal fluid by tuberculous exudate; the inability of antimicrobial agents to penetrate avascular tissue and reach tubercle bacilli buried therein; and the necessity of prolonged intrathecal therapy that may, of itself, produce local obstructions in the subarachnoid space by repeated irritation and trauma of the meninges. It is generally conceded that all the newer measures devised to counteract these effects — namely, anticoagulants,[1] intrathecal injection of tuberculin,[2, 3] fibrinolytic enzymes [4, 5] and neurosurgical procedures — have met with equivocal success. A previous communication[6] described a case of tuberculous meningitis treated with cortisone and streptomycin, without intrathecal therapy. When this treatment was instituted, the prognosis was considered hopeless; nevertheless, today (more than eighteen months later) the patient is clinically well and at home. If this result could be reproduced in a series of cases, it would indicate that the morbid conditions outlined above, which militate against recovery in tuberculous meningitis, are not irreversible. The purpose of this paper is to present a series of case reports that reproduce most of the results described in the original publication.

MATERIAL AND METHODS

The reports given in brief outline below describe a group of unselected cases of tuberculous meningitis in patients consecutively admitted to Point Edward Hospital between October 1, 1951, and the date of submission of this manuscript. All patients were transferred to this institution for treatment from other hospitals, where the diagnosis had previously been established. It should be emphasized at the outset that no predetermined scheme of treatment was followed, and that each case was reviewed at frequent intervals, with such changes in medication and management as were indicated at the time of review. As a general rule, however, treatment was usually begun with 200 to 300 mg. of cortisone daily, by mouth when practicable, but intramuscularly when oral administration was impossible. This was usually accompanied by the intramuscular administration of streptomycin or dihydrostreptomycin, 1.0 gm. daily, and PAS (para-aminosalicylic acid) by the oral route to tolerance. In 1 case (Case 6), however, streptomycin was withheld because of a history of severe hypersensitivity, and was replaced by full doses of isoniazid; in another (Case 3), all three antimicrobial agents were used. It should also be stressed that no intrathecal streptomycin therapy was used in this series, with the exception of 1 case (Case 3), in which intrathecal injections were given for a short period.

The original daily dosage of cortisone was maintained in every case until there was decided improvement in the clinical and laboratory findings, and then gradually diminished by decrements of 50, 25 or 10 mg., depending on the dosage that the patient was receiving at the time of review. In no case was a specific daily dosage maintained for less than two weeks, and in all cases a final dosage of 5 to 10 mg. daily was continued for varying periods before the drug was finally discontinued. Antimicrobial therapy with one or more drugs was carried on for three to six months after cortisone had been discontinued. Attempts were also made, with a fair degree of success, to adjust streptomycin dosage in such a manner as to prevent eighth-nerve damage.

In view of the known propensity of cortisone to reactivate apparently healed tuberculous lesions, serial x-ray examinations of the chest were made at intervals of two weeks. In accordance with present-

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day concepts of dietary management in cortisone therapy[7] all patients were maintained on a diet high in protein and fat, low in carbohydrate and low in sodium. Supplementary potassium chloride was provided in amounts up to 6.0 gm. daily. Weekly urinalyses were carried out to detect glycosuria. Spinal-fluid examinations were made several times weekly in the early phases of treatment, but, as improvement became evident, the interval was lengthened to two weeks. As indicated above, adjustments in therapy were guided by the results of spinal-fluid examination and frequent clinical assessment.

Case Reports

Case 1. O.B., a 28-year-old woman, was admitted to the hospital on October 1, 1951, with bacteriologically proved tuberculous meningitis. Four weeks of intensive treatment with intramuscular injections of dihydrostreptomycin, 2.0 gm. daily, intrathecal administration of streptomycin, 50 mg. daily, and PAS by mouth, 10.0 gm. daily, had had no beneficial effect. Evidence of a lumbar intrathecal block had developed, and, by October 29, the block had become complete, and it was impossible to enter the spinal theca by the lumbar route. After a cisternal puncture and the instillation of streptomycin and streptokinase-streptodornase by this route, the patient became gravely ill, and, within a few hours, appeared moribund. Cortisone therapy was begun on November 12 in a dosage of 300 mg. daily, concurrently with intramuscular injections of streptomycin and PAS by mouth. Clinical improvement was obvious within 48 hours, and has continued to the present. Most important, however, is the fact that, apparently as a result of treatment, the lumbar intrathecal block early gave signs of resolution, and had completely disappeared by January 17, 1952, when, 11 weeks after the beginning of cortisone therapy, lumbar puncture was attended by a free flow of spinal fluid. The dose of cortisone was gradually decreased, as outlined above, over 1 year, the hormone finally being discontinued on October 16, when the patient had received a total of 33.7 gm. This was at all times covered by adequate dosage of streptomycin and PAS, and no intrathecal therapy was given. At present, the patient is receiving no antimicrobial agents, her spinal fluid is normal, and she is clinically well and has been discharged to her home. It should be noted that this patient is the subject of our original report.[6] Representative spinal-fluid findings are presented in Table 1.

Table 1. *Representative Spinal-Fluid Findings in Case 1.*

Date	White Cells per cu. mm.	Protein mg./100 cc.	Chloride mg./100 cc.
Oct. 2, 1951	550	205	580
Nov. 12, 1951	(Cortisone therapy begun)	—	—
Dec. 3, 1951	70	82	710
July 7, 1952	19	75	700
Mar. 3, 1953	3	32	700

Case 2. F.M., a 9-month-old girl, was admitted to the hospital on December 17, 1951, with primary tuberculosis, and tuberculous meningitis corroborated by bacteriologic examination of the spinal fluid before admission. Treatment was begun immediately with dihydrostreptomycin, 0.5 gm. intramuscularly twice a day, PAS, 4.0 gm. daily, and daily intrathecal injections of streptomycin, until January 21, 1952, when it became difficult to enter the lumbar theca. On that date, examination of the spinal fluid revealed a spider-web clot and a protein content of 540 mg. and a chloride concentration of 660 mg. per 100 cc. (the protein content on admission had been 215 mg. per 100 cc., and had fallen to 160 mg. immediately before this date). These facts, together with the finding that the spinal fluid was distinctly yellow and readily coagulable, strongly suggested the development of a block. On January 31 intrathecal therapy was discontinued, and treatment was begun with cortisone acetate, 200 mg. daily, by the oral route; intramuscular injection of streptomycin and PAS by mouth were continued. This treatment resulted in rapid and continued improvement in the cytologic and chemical findings in the spinal fluid (Table 2). The dosage of cortisone was gradually decreased, and the drug was finally discontinued on November 30.

Table 2. *Representative Spinal-Fluid Findings in Case 2.*

Date	White Cells per cu. mm.	Protein mg./100 cc.	Chloride mg./100 cc.
Dec. 19, 1951	180	215	720
Jan. 8, 1952	117	160	700
Jan. 21, 1952	(Cell count impossible because of fibrin clot)	540	660
Jan. 31, 1952	(Cortisone therapy begun)	—	—
Feb. 18, 1952	97	75	760
May 6, 1952	20	60	780
Oct. 8, 1952	5	15	740
Feb. 28, 1953	5	15	760

At present the patient is being treated with PAS alone; the spinal fluid is normal, and, although she suffers from deafness, probably the result of streptomycin therapy, she is otherwise clinically well.

Case 3. R.J., a 12-year-old boy, was admitted to the hospital on April 16, 1952, as a transfer from another hospital, where he had been treated with burr holes and intraventricular administration of streptomycin. At the time of admission he had received 7 months' treatment by this route, as well as intramuscular injections of streptomycin and PAS by mouth in the usual dosage. On admission the spinal fluid was normal, and he was clinically well. However, approximately 1 month after admission, he became violently ill, with severe headache, nausea, vomiting and bulging of the soft tissues over the burr holes. Spinal fluid collected on that date was found to be under increased pressure and to contain 77 white cells per cubic millimeter and 82 mg. of protein and 660 mg. of chloride per 100 cc. A specimen of spinal fluid collected 1 week before this episode grew tubercle bacilli on culture after 12 weeks' incubation. Cortisone therapy was begun on May 14 in a dosage of 250 mg. daily, given orally. Intramuscular injections of streptomycin and PAS by mouth were continued in adequate dosage. Slight improvement occurred for approximately 2 months, but this was not striking and recovery was considered in doubt. On July 15 isoniazid therapy was begun in a dosage of 100 mg. daily, which was gradually increased to 300 mg. daily. Cortisone, 150 mg. daily, streptomycin, 1 gm. intramuscularly a day and 50 to 100 mg. intrathecally 3 times weekly, and PAS, 10.0 gm. daily by mouth, were continued. On this regimen, improvement in the clinical and laboratory findings (Table 3) has been gradual and continuous, and at present the patient is clinically well. Treatment now consists of cortisone, 5 mg. daily, PAS 10 gm. daily, and isoniazid, 300 mg. daily, all by mouth. Streptomycin intrathecally was discontinued on November 17, and intramuscular injections on January 2, 1953.

Table 3. *Representative Spinal-Fluid Findings in Case 3.*

Date	White Cells per cu. mm.	Protein mg./100 cc.	Chloride mg./100 cc.
Apr. 24, 1952	2	21	700
May 14, 1952	77	82	660
May 14, 1952	(Cortisone therapy begun)	—	—
July 14, 1952	64	70	640
July 14, 1952	(Isoniazid therapy begun)	—	—
Aug. 22, 1952	9	100	620
Dec. 19, 1952	6	27	760
Feb. 16, 1953	0	18	760

Case 4. M.MacI., a 9-year-old boy, was admitted to the hospital from another hospital on May 31, 1952, for the treatment of tuberculous meningitis. He had received a few doses of streptomycin intramuscularly before admission, and tubercle

bacilli were not recovered from the spinal fluid. The diagnosis was therefore established on the basis of clinical findings, and the cytologic and chemical characteristics of the spinal fluid. On admission, the patient was delirious, semicomatose and unmanageable; examination of the spinal fluid revealed 195 white cells per cubic millimeter and 225 mg. of protein and 620 mg. of chloride per 100 cc. Treatment was begun immediately with 200 mg. of cortisone, 1.0 gm. of streptomycin intramuscularly and 10.0 gm. of PAS by mouth daily. Within 10 days he was alert, co-operative and generally much improved, with spinal-fluid findings of 79 white cells per cubic millimeter and a protein of 108 mg. and a chloride of 700 mg. per 100 cc.

TABLE 4. *Spinal-Fluid Findings in Case 4.*

DATE	WHITE CELLS *per cu. mm.*	PROTEIN *mg./100 cc.*	CHLORIDE *mg./100 cc.*
June 1, 1952	195	225	620
June 11, 1952	79	108	700
July 20, 1952	30	60	700
Sept. 26, 1952	10	40	700
Dec. 19, 1952	9	30	780
Mar. 19, 1953	2	22	700

The dosage of cortisone was gradually decreased, and the hormone was finally discontinued on February 26, 1953. Streptomycin is being continued in a dosage of 0.5 gm. twice weekly, with PAS daily. The spinal fluid was normal and the patient was clinically well when last seen. Serial chest films at intervals of 2 weeks have revealed no pulmonary disease.

Representative spinal-fluid findings are presented in Table 4.

CASE 5. A.M., an 18-month-old Indian girl, was admitted to the hospital on June 15, 1952, as a transfer from another hospital, where a diagnosis of tuberculous meningitis had been made. On admission she appeared moribund, exhibiting what was described as "decerebrate rigidity." X-ray examination of the chest revealed a wedge-shaped density in the right-lung field, suggestive of a primary tuberculous lesion, and there were also questionable miliary nodules throughout both lung fields. Examination of the spinal fluid showed 8 white cells per cubic millimeter, with a protein of 120 mg. and a chloride of 620 mg. per 100 cc. Treatment was immediately begun with cortisone, 300 mg., and streptomycin, 1.0 gm., daily, both intramuscularly. No improvement was noted, and the patient died without having regained consciousness 2 weeks after admission. Autopsy disclosed a caseous, cavernous tuberculous lesion of moderate severity in the right lung, apparently extending laterally from the hilus. The left lung gave no gross evidence of tuberculous disease. Close examination of the brain revealed flattening of the convolutions, particularly on the right. At the base of the brain, in the interpeduncular fossa, was a thin layer of gummy exudate of the type usually associated with tuberculous meningitis. The right cerebral hemisphere was reddened and extremely friable. After prolonged fixation in formol saline solution it was sectioned. The cut surface showed a purplish, discolored area occupying about a third of the entire hemisphere and situated closer to the occipital than to the frontal pole. The material comprising this area was still extremely friable, despite fixation. Microscopical examination of sections of the lung demonstrated caseous tuberculous foci, which presented a general picture of inactivity with little cellularity and much fibrosis. A number of miliary tubercles were also seen in which there were caseous centers without the usual epithelioid congeries and a scant cellular reaction. Examination of sections of the spleen showed numerous miliary foci of similar pattern to those noticed in the lungs. Examination of sections from the base of the brain disclosed a layer of loose fibrin clot and granulation tissue. The vessels in the meninges demonstrated endarteritis. The picture was that of tuberculous meningitis, except that the cellular exudate was small. Examination of the right cerebral hemisphere revealed masses of structureless, hyaline material, which was considered to represent cerebral infarction (Fig. 1).

CASE 6. Mrs. A. MacD., a 36-year-old woman, was admitted to the hospital on October 28, 1952, as a transfer from another hospital, where she had received 3 months' treatment for tuberculous pleurisy with effusion; a severe and persistent headache had suddenly developed a few days before admission. Shortly before entry, she had had several severe (one almost fatal) convulsive reactions to streptomycin, and it was considered unwise to continue the administration of this drug. Examination of the spinal fluid revealed 60 white cells per cubic milli-

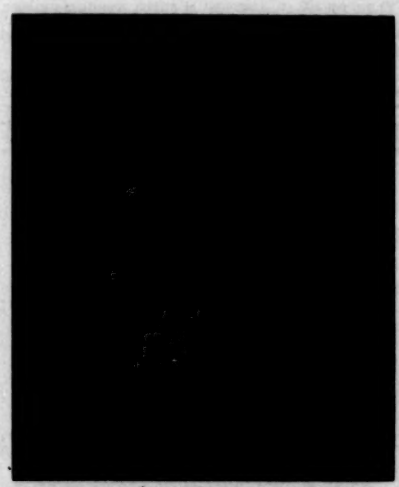

FIGURE 1. *Section of the Brain in Case 5 Showing Almost Complete Infarction of the Right Cerebral Hemisphere.*

meter, with a protein of 126 mg. and a chloride of 740 mg. per 100 cc. Within a week, however, the values were 280 white cells per cubic millimeter and 256 mg. of protein and 620 mg. of chloride per 100 cc. Tubercle bacilli were found in the spinal fluid, both on direct smear and on culture after 4 weeks' incubation. In view of the history of extreme hypersensitivity to streptomycin, treatment was begun with cortisone, 300 mg.

TABLE 5. *Spinal-Fluid Findings in Case 5.*

DATE	WHITE CELLS *per cu. mm.*	PROTEIN *mg./100 cc.*	CHLORIDE *mg./100 cc.*
Nov. 1, 1952	280	256	620
Nov. 2, 1952	(Cortisone, isoniazid and PAS begun)	—	—
Nov. 5, 1952	96	178	620
Nov. 25 1952	13	49	700
Jan. 5, 1953	1	57	700
Jan. 27, 1953	100	55	760
Feb. 4, 1953	(Dihydrostreptomycin added)	—	—
Feb. 25, 1953	50	57	840
Mar. 9, 1953	13	45	800
Mar. 23, 1953	5	51	700

daily, isoniazid, 600 mg. daily (10 mg. per kilogram of body weight), and PAS, 13.5 gm. daily. On this regimen, with decreasing doses of cortisone, she did well, and, on January 5, 1953, examination of the spinal fluid showed 1 white cell per cubic millimeter, with a protein of 57 mg. and a chloride of 700 mg. per 100 cc. However, on January 10, persistent elevation of temperature began to occur, finally reaching 101°F., and,

on January 27, examination of the spinal fluid demonstrated 100 white cells per cubic millimeter. Dihydrostreptomycin, 1.0 gm. daily by intramuscular injection, was added to the therapeutic regimen, without untoward effect, and the temperature gradually fell to normal. Within 2 weeks the white cells in the spinal fluid had fallen to 30 per cubic millimeter, and on last examination the cerebrospinal fluid contained 5 white cells per cubic millimeter, with a protein of 51 mg. and a chloride of 700 mg. per 100 cc. Treatment at present consists of cortisone, 50 mg. daily, dihydrostreptomycin, 1.0 gm. twice weekly, PAS 13.5 gm. daily, and isoniazid, 600 mg. daily. Representative spinal-fluid data are presented in Table 5.

Case 7. C. M., a 31-year-old man, was admitted to the hospital on January 25, 1953, as a transfer from another hospital, with a 2-week history of headache, dizziness, nausea and fever. On admission he was semicomatose and irrational, and examination of the spinal fluid revealed 225 white cells per cubic millimeter, with a protein of 232 mg. and a chloride of 580 mg. per

Figure 2. *Section from the Base of the Brain In Case 7, Showing Tremendous Thickness of Exudate (X15).*

100 cc. Treatment was immediately begun with cortisone 200 mg. daily, streptomycin 1.0 gm. (later 2.0 gm.) daily by the intramuscular route, and PAS 13.5 gm. daily by mouth. A chest film revealed fine miliary nodules throughout both lung fields. Despite intensive therapy there was no improvement, either clinically or in the laboratory findings, and the patient died suddenly 12 days after admission. At autopsy the most striking gross findings were in the brain, which showed a mild degree of symmetrical internal hydrocephalus. There was a thick, gummy, greenish exudate at the base of the brain in the interpeduncular space and around the brain stem. This exudate, was, in places, almost 0.6 cm. in thickness (Fig. 2). Microscopical examination of sections of the brain showed typical exudate formed of blocks of fibrin and tuberculous granulation tissue, the vessels of which showed endarteritis. An unusual feature of this exudate was that it demonstrated a sparse cellular reaction. Sections of the liver showed fairly numerous foci, presumably tuberculous nodules, composed mostly of structureless hyaline material, sparsely infiltrated with lymphocytes. Sections of spleen revealed a number of tiny "inactive" miliary tuberculous follicles. Microscopical examination of sections of lung disclosed numerous miliary tubercles that had a hyaline appearance.

Discussion

This series of case reports provides evidence that the addition of cortisone therapy to antimicrobial regimens in the treatment of tuberculous meningitis may simplify the management and improve the prognosis in this serious disease. It is, of course, impossible to prove that the beneficial results obtained in any given case can be ascribed to the cortisone therapy. For example, in Case 1 cortisone therapy was begun only three days after the intracisternal instillation of streptokinase-streptodornase, and the resolution of the block could be ascribed to the enzyme therapy rather than to the cortisone. However, only a single instillation of enzymes was carried out, and the resolution of the block followed eleven weeks of cortisone therapy. Under these circumstances, it seems more likely that the resolution of the block was brought about by the cortisone therapy than by enzymatic débridement. In Case 2 we were, of course, unable to establish, beyond doubt, the presence of a block. However, by January 21, 1952, it had become increasingly difficult to enter the spinal theca, and the sudden rise in spinal-fluid protein, together with the finding of a yellow and readily coagulable spinal fluid, strongly suggests the occurrence of this complication. In Case 3 the most dramatic change in the clinical course occurred after isoniazid therapy had been begun, and it is more than probable that this chemotherapeutic agent strongly influenced the final satisfactory result. However, a period of two months elapsed between the diagnosis of relapse and the institution of isoniazid therapy. During that period, cortisone therapy was given in conjunction with streptomycin and PAS, and it seems unlikely that the patient would have survived for this two-month period on streptomycin and PAS therapy alone (that is, without cortisone).

It is in the early stages of therapy that we have noted the most striking effects, apparently from the addition of cortisone to the therapeutic regimen. In several cases there has been an early and dramatic clinical response in our cortisone-treated patients as compared with those who have received only conventional therapy.

As indicated above in the section on "Material and Methods," these results have been obtained almost exclusively without the intrathecal administration of streptomycin. For several reasons we consider this an important advance in the treatment of tuberculous meningitis. In the first place, the avoidance of repeated needle trauma to the meninges may be a prime factor in preventing the occurrence of subarachnoid block. Secondly, the performance of frequent spinal punctures is highly uncomfortable to the patient and extremely tedious for medical personnel, and the intrathecal administration of streptomycin has its own potential dangers.[8] Any therapeutic regimen, therefore, that makes this procedure unnecessary constitutes, in our opinion, a material advantage.

There have been frequent references in the literature[9-12] to the reactivation of quiescent or healed

tuberculous lesions in the lungs as a result of cortisone therapy for conditions unrelated to tuberculosis. It was for this reason that x-ray examination of the chest was carried out at fortnightly intervals in all patients in this study. No evidence of the development or reactivation of tuberculous pulmonary disease was noted in any case in this series; on the contrary, in the 2 cases in which autopsy was performed, histologic evidence of regression was noted in the miliary lesions in all organs examined. It is our opinion that the dangers of cortisone therapy in tuberculous meningitis are mitigated, if not entirely dispelled, by an intensive concurrent antimicrobial regimen.

As was to be expected, evidence of hypercortisonism in the form of a Cushing's syndrome of greater or less degree appeared in all patients under prolonged steroid therapy. However, this complication has uniformly disappeared as cortisone dosage has been decreased or terminated.

In no case did permanent diabetes occur, although transient slight glycosuria was noted in a few.

FIGURE 3. *Section of Exudate in a Case of Tuberculous Meningitis, Treated by Conventional Methods, without Cortisone (X50).*
Note the marked cellularity and intense inflammatory reaction.

Cases 3 and 4 deserve special mention, since they illustrate an important factor in success of therapy — namely, that cortisone treatment must be accompanied by adequate dosage of antimicrobial agents to which the patient's tubercle bacilli are sensitive. In Case 3 it seems highly probable that a degree of bacterial resistance to streptomycin had developed before cortisone therapy, since it was not until isoniazid was added to the treatment regimen that striking improvement began. In Case 6 the situation was apparently reversed in that, despite isoniazid and PAS therapy, a probable relapse occurred, dihydrostreptomycin being required for control. It seems clear, therefore, that the success of cortisone therapy is contingent upon the provision of adequate and effective antimicrobial coverage.

It appears important at this point to review the information provided by autopsy in Cases 5 and 7. It seems clear that the cause of death in Case 5 was massive infarction of the right cerebral hemisphere (Fig. 1). Extensive and careful examination of the brain failed to disclose any major arterial

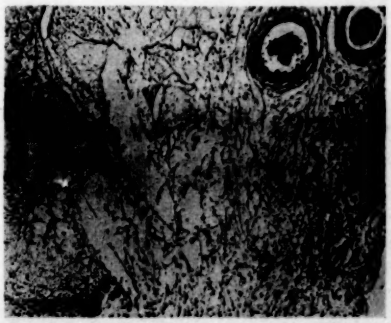

FIGURE 4. *Section of Exudate from the Base of the Brain in a Patient with Tuberculous Meningitis Treated by Cortisone and Antimicrobial Agents (X50).*
Note the marked acellularity and virtual lack of inflammatory reaction.

occlusion, and there is no evidence that the cerebral necrosis and the cortisone therapy were in any way related. There is precedent in the recent literature, however, for the occurrence of massive necrosis of nervous tissue as a complication of tuberculous meningitis. Recently a case of diffuse tuberculous meningitis and meningomyelitis with marked necrosis of spinal-cord tissue, resulting in a paraplegic syndrome was reported.[13] It requires no great stretch of the imagination to transfer these findings to a cerebral hemisphere, in whole or in part. In any event no known form of therapy could have been expected to bring about recovery in the presence of cerebral damage of such magnitude. In Case 7 the outstanding finding at autopsy was a mass of tenacious, gelatinous exudate approaching 7 mm. in thickness, in and around the interpeduncular fossa (Fig. 2). This implies considerable duration of disease before treatment, which could hardly have been expected to be effective against such odds. It is becoming increasingly evident that, in tuberculous meningitis as in cancer, early diagnosis and early institution of specific therapy are essential for a successful outcome.

In our original communication[6] we suggested, on theoretical grounds, that the benefits that might accrue from cortisone therapy in tuberculous menin-

gitis would be based on the known ability of this adrenal steroid to suppress the inflammatory process, or to bring about its reversal.[14] This has been borne out by our own histologic studies (Fig. 3 and 4), of the tuberculous exudate and other tissues (Fig. 5), in our autopsied cases, which reveal a striking lack of cellularity in the tissues and exudates of patients treated with cortisone, as compared with sections from cases treated by conventional methods. It is highly probable that this suppressive action on exudate formation is the prime factor in preventing the sealing off of the strategic foramens at the base of the brain, which frequently results in irreversible hydrocephalus.

FIGURE 5. *Section of the Liver in Case 7 Showing a Miliary Tubercle (X50).*

This tubercle gives evidence of "regression," in that it is much less cellular than such lesions usually are.

In view of the fact that our series of cases is small, and the follow-up period relatively short, this must be considered as an interim report. The short-term results, however, are highly encouraging. It is our opinion, therefore, that combined therapy of tuberculous meningitis with cortisone and antimicrobial agents has distinct promise and is worthy of further and more extensive clinical trial.

SUMMARY AND CONCLUSIONS

Seven cases of tuberculous meningitis treated with combined cortisone and antimicrobial agents, with recovery in 5, are reported. In 1 case the resolution of an established subarachnoid block occurred during treatment, and in another, there is evidence that the development of an incipient block was suppressed by cortisone.

In 1 case clinical and bacteriologic relapse, which had occurred after neurosurgical treatment (burr holes), was reversed by this form of combined therapy.

The theoretical basis for this form of treatment is discussed in relation to the autopsy findings in 2 cases treated in this manner.

The use of cortisone in the presence of active tuberculosis appears to be a safe procedure, provided that it is adequately covered by effective antimicrobial therapy.

The importance of early diagnosis and early institution of treatment is again emphasized, and further clinical trial is recommended.

Since this paper was submitted for publication, 2 additional cases of tuberculous meningitis have been treated at this institution under the same regimen. Although it is too early to predict the eventual outcome, both patients have shown the same early and striking clinical and laboratory improvement described above. In addition, 2 patients[15] with tuberculous meningitis have been treated by this regimen in another institution under our supervision. These patients had had thorough trial on conventional therapy, and the illness was following a downhill course. Clinical and laboratory improvement began very shortly after the institution of cortisone therapy and has been maintained to date.

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THE INFLUENCE OF WEIGHT REDUCTION ON AMENORRHEA IN OBESE WOMEN*

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A STATISTICAL study of 100 women with menstrual disorders showing a significant increase in the incidence of obesity in women with amenorrhea was reported from this clinic in July, 1952.[1] Of 60 women without periods for at least three months, 29, or 48 per cent, were obese. The incidence of obesity in a control group of women of similar age range was 13 per cent. During the course of this study, several obese women who lost weight had a return of menses. The beneficial effect of weight reduction in amenorrhea has been a well known clinical observation, but, apparently, no series of cases with weight reduction alone as a therapeutic measure has been reported. It is the purpose of this paper to present our experience with a group of obese women with amenorrhea in whom weight reduction was attempted.

METHODS

Thirty-two obese women with amenorrhea were followed long enough for the possible effect of weight reduction on restoration of menses to be observed. Amenorrhea was defined, as in the previous study, as the absence of menses for at least three months at the time the patient first came under observation. Obesity was defined as a weight of 20 per cent or more above ideal weight according to standard nomographs.[2] Keys[3] has commented on the problems encountered in the use of such standards. It was believed, however, that if the 20 per cent overweight figure was selected as a minimal requirement, the patients under observation would be considered obese by any criteria. The longest period of observation was thirty-one, and the shortest three months. One patient who had infrequent staining and 2 patients who menstruated on the day of pelvic examination after a lapse of menses for eleven months and seven months were included in the study. The patients were seen on admission to the New England Center Hospital, Pratt Diagnostic Clinic or Boston Dispensary, and each patient was given a 1200-calorie diet, instructed in its use and informed of the possible beneficial effects of weight loss. Follow-up visits were scheduled for most of the patients, the remaining few being reported on by letters from either the physician or the patient.

In none of these patients was there any pelvic disorder or systemic disease to account for the amenorrhea. The incidence of psychiatric diagnoses was high.

RESULTS

In 32 patients sufficient data were obtained to indicate the effects of a therapeutic regime. The group ranged in age from seventeen to thirty-eight years. All were at least 20 per cent above ideal weight, and 20 women weighed 50 per cent or more above ideal weight. Follicle-stimulating-hormone determinations were made on the urine in 25 cases and were normal in all. It was believed that in these patients the amenorrhea should be classified as "hypothalamic," according to Reifenstein's[4] definition of the term.

Thirteen of the 32 patients lost weight and coincidentally began to menstruate. The duration of amenorrhea in this group varied from three to thirty-six months. Two patients had each had one pregnancy, and 1 had had two pregnancies. Ten were 50 per cent or more above ideal weight. The amount of weight lost ranged from 13 to 69 pounds during the period of observation. An attempt was made to correlate the time of return of menses to the time required to lose weight. In each of these cases weight loss coincided in time with return of menses. Menses returned at intervals of one to four months after the 1200-calorie diet had been started. The return of menses was in most cases well before the total weight loss had occurred and in 2 after a loss of 7 and 8 pounds. Four patients became pregnant, 3 for the first time. One of these patients, 23 per cent overweight, had had no periods for seventeen months. One month after her first visit and well before her total weight loss, she began to menstruate and shortly thereafter became pregnant. After delivery, she again had amenorrhea of eleven months' duration. Another patient, 95 per cent overweight and with amenorrhea of six months' duration, menstruated a month after losing 7 pounds. In two months, she had lost a total of 20 pounds, but regular menses did not return for another six months. A patient who was 75 per cent overweight and without menses for eleven months menstruated on the day she was examined. Another, who was 55 per cent over ideal weight, lost 15 pounds, had a period in a month and another three months later. She then regained her weight and has had amenorrhea for the past six months. One patient with no periods for two years lost 15 pounds in a month resumed menstruation, had a miscarriage in six months

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and a delivery at term ten months later. These results are shown in Table 1.

Fifteen of the 32 patients failed to lose weight and also failed to menstruate. Two of these received estrogens from other physicians, with temporary withdrawal bleeding. All in this group continued to have amenorrhea or oligomenorrhea, and none became pregnant.

It is significant that only 2 patients lost weight without coincident return of menstruation. In that those who lost weight and resumed menstrual function were women in whom the patient-doctor relation, laboratory tests and reassurance about the absence of serious disease were effective psychotherapeutic measures. That obesity and amenorrhea are both symptoms of a basic emotional problem seems likely. It is widely accepted that obesity may be the result of an emotional disorder,[5, 6] and likewise the concept of psychogenic amenorrhea has recently achieved clinical recognition. The fact

TABLE 1. *Data on Patients Who Lost Weight and Whose Periods Returned.*

Subject	Parity	Height	Weight	Over-weight	Duration of Amenorrhea	Weight Loss		Return of Menses	Comment
						at onset of menses	total		
		in.	lb.	%	mo.	lb.	lb.		
E. B.	1	66	260	88	11	23	63	After 4 mo.	Regular periods
E. N.	0	63	201	58	36	?	40	After 2-3 mo.	Patient became pregnant but miscarried
L. G.	0	68	198	36	10	12	18	After 2 mo.	Regular periods
La F.	0	62	152	23	17	?	25	After 1 mo.	Patient became pregnant
I. L.	1	65	261	95	6	7	70	After 1 mo.	Weight 235 in 2 mo.; no periods again till 6 mo. later.
S. Mc.	0	66	240	75	11	0	50	On day of examination	Regular menses for 7 mo. followed by amenorrhea for 6 mo.
A. P.	0	66	200	39	15 (oligomenorrhea 9 months)	30	30	After 2 mo.	—
M. P.	0	64	200	54	24	?	31	After 3-4 mo.	—
F. R.	2	61	244	102	3	16	56	After 1 mo.	Patient became pregnant
M. R.	0	57	177	55	2	15	15	After 1 mo.	2d period 2 mo. later; patient regained weight and had no periods for next 6 mo.
A. S.	0	62	160	29	12	18	30	After 3 mo.	Ovulatory periods
V. G.	0	66	237	72	10-12	?	69	After 2 mo.	Periods every 2 mo.
Lec.	0	63	208	59	24	15	28	After 1 mo.	Miscarriage 6 mo. later; term pregnancy 16 mo. later.

2 cases periods returned without any loss of weight, and in 1 of these, menstruation occurred on the day of examination after seven months of amenorrhea. Subsequently, after a 13-pound weight loss, cyclic vaginal bleeding was reported.

Discussion

The results of this study indicate that in the obese woman with amenorrhea, weight reduction alone may be an effective therapeutic measure resulting in return of menstrual periods as evidenced by the fact that 13 of 15 obese women with amenorrhea who lost weight resumed menses, whereas 15 obese women who failed to lose weight were not affected.

A closer scrutiny of the sequence of events in patients who lost weight and began to menstruate suggests that the onset of the menses frequently precedes any marked loss of weight and occurs so soon after the start of the therapeutic regimen that the absolute degree of obesity cannot be the only factor involved. The observations fit better with the concept that a return of the menstrual cycle coincides with a decreasing body weight, and perhaps the beneficial effect is in some way mediated by the negative caloric balance. It is also possible that both symptoms improved at about the same time suggests that a common emotional factor may be responsible. Why half the patients under observation responded satisfactorily and the remaining half failed to improve is not clear. We are unaware of any difference in the therapeutic regimen, approach or management of the two groups, and the only factor that correlated well with a return of menstrual periods was the loss of body weight. Several of the patients in the two groups had psychoneuroses. In some cases the obesity and amenorrhea seemed to be related to disturbing situational problems.

Summary and Conclusions

Obesity and amenorrhea have previously been shown to be commonly associated clinical symptoms. In nearly half of a series of 32 obese women with amenorrhea, weight reduction and resumption of normal menses were accomplished. The prompt onset of menses, which in several cases occurred before a significant amount of weight had been lost, indicates that the decreased obesity is not the only factor concerned in the restoration of the menstrual cycles but that a negative energy balance

may exert a favorable influence. It is also possible that obesity and amenorrhea are coincident symptoms of a basic emotional disorder that may respond to formal psychotherapy or to friendly interest and simple reassurance.

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THE CARDIOVASCULAR EFFECTS OF CERVICOTHORACIC VAGECTOMY IN THE HUMAN BEING*

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IN the normal human being, vagal impulses are thought to affect the heart in the following ways: by decreasing the rate of production of impulses by the sinoatrial node, by prolonging the atrioventricular conduction time and by diminishing the force of atrial and ventricular contraction.

In the first instance, slowing of impulse production by the sinoatrial node is ultimately due to afferent stimuli from the aortic arch, the carotid sinus and the great veins of the atria. Numerous other sites have been thought to initiate afferent impulses that cause cardiac slowing. These afferent stimuli, from whatever source, converge on the cardiac center, which, in turn, acts on the heart via the vagus nerves. It is assumed that the cardiac rate in the normal human being is regulated by a tonic vagal action that waxes or wanes according to the physiologic requirements of the organism.

The role of stimuli transmitted via the sympathetic system is less clear. Such stimuli tend to increase cardiac rate and are opposed by vagal stimuli, the final rate being due to the balance between the two. Of the two effects, the vagal is generally said to be the more important[1] although, as shown by Smithwick and his co-workers,[2] increase in pulse rate in response to exercise is due not merely to vagal inhibition but also to sympathetic stimulation.

Much of the existing knowledge concerning the action of the vagus nerves on the heart stems from animal experimentation. Bilateral extirpation of the cervical and high thoracic portions of the vagus nerves in laboratory animals is said to produce a fatal issue owing to the development of pulmonary edema,[3] among other complications. The effects of a similar procedure in man have not, to our knowledge, been described, although several reports regarding unilateral cervicothoracic vagectomy are available.[4-6] The following case is apparently unique in that vagectomy was complete on one side and nearly complete on the other.

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Case Report

A 40-year-old farmer was referred to the hospital because of the presence of mediastinal masses in a survey chest film. He had no complaints of any kind. He had been carefully investigated at another hospital before referral, but the results of these studies did not disclose the nature of the abnormality.

Physical examination showed nothing of diagnostic significance. Examination of the blood, including an erythrocyte sedimentation rate, and of the bone marrow revealed normal findings throughout. An inguinal lymph node was also normal morphologically.

X-ray films of the chest showed nodular soft-tissue masses projecting bilaterally from the mediastinum at the level of the aortic arch. The masses did not pulsate abnormally, and neither the trachea nor the esophagus was deviated.

Pulse rates and blood-pressure readings are given in Table 1.

On January 29, 1953, thoracotomy was carried out by Dr. C. W. Lillehei, and multiple tumors of both vagus nerves were found. On the left, they began at the origin of the recurrent laryngeal nerve and extended upward to the level of the carotid bifurcation. On the right, the lowest mass lay behind the superior vena cava just as it entered the right atrium. Tumor masses were also seen as high as the origin of the right subclavian artery, but exploration was not carried beyond this point. The tumors varied from small nodules to large masses that were "almost egg size." Between the tumor masses, and below the lowest ones, the vagi seemed to be normal. On the left, the tumors and the vagus were removed as completely as possible, the recurrent laryngeal nerve being sacrificed in the process. On the right, tumors and nerve were removed up to a point

Table 1. *Blood Pressure and Pulse Rate (Resting) before and after Bilateral Vagotomy.*

Date	Pulse Rate	Blood Pressure
2/29/52	80	116/76
1/22/53	72	120/68
1/29/53*	80	140/78
1/29/53†	120	122/70
1/30/53	128	140/94
1/31/53	136	118/80
2/5/53	130	142/70
2/18/53	120	140/95
4/1/53	120	140/95
6/3/53	120	140/92

*Before operation.
†After operation.

about 3 mm. below the origin of the recurrent laryngeal nerve, the latter (and tumor masses higher in the thorax and neck) being left undisturbed.

Gross examination of the surgical specimens showed that the largest (from the left side) was 16 cm. long and had a maximal diameter of 2.5 cm. An attached portion of nerve trunk could be traced some distance into the mass. Microscopically, the appearance was that of neurofibroma. The tumors were made up of small, spindle-shaped cells scattered through an edematous, reticular stroma. There was a thin fibrous capsule. A portion of nerve trunk could be seen in one of the blocks, and in some areas portions of the tumor actually lay within the trunk.

During operation, the pulse rate abruptly increased from 80 to 120 per minute. Simultaneously, the blood pressure fell slightly but returned to normal when vasopressor drugs were administered. Otherwise, the operative course was not remarkable.

Postoperatively, the complications were few although the pulse rate remained elevated (Table 1). It was also discovered that paralysis of the left vocal cord had developed. In addition the patient complained of epigastric fullness, belching and loose stools, all of which were relieved by Urecholine. Apart from these items, he recovered completely and was soon back at active farming.

Physiologic Studies

Because most of the normal efferent parasympathetic pathways to the heart were interrupted at operation, it was thought pertinent to study the changes brought about by exercise in cardiac rate, blood pressure and cardiac output. The determinations were made about four months after operation. Cardiac output was measured by use of the Evans blue dye technic described by Hamilton but with certain modifications.[7] The resting output was determined on the fasting patient while he lay quietly in bed. Arterial blood samples were collected through a polyethylene catheter, the proximal end of which lay in the brachial artery. Initial blood-pressure measurements were made through the catheter with the patient standing on a motor-driven treadmill. Recording was by means of a satisfactorily damped system consisting of a Statham strain gauge (15 lb. per square inch) and a Sanborn polyviso recorder. The subject then walked for ten minutes at 3 miles per hour on the treadmill, which was adjusted to a 5 per cent grade. A second measurement of cardiac output was made exactly at the end of the ten-minute exercise period, but the exercise was not interrupted for the procedure. On completion of the second dye-curve determination, a record of the blood pressure was begun and was continued until one minute after cessation of exercise. Further records of the blood pressure were made during the first twenty seconds of each succeeding minute for five minutes.

After the patient had returned to bed and was completely rested from the exercise, 0.6 mg. of atropine sulfate was given subcutaneously. There was no change in pulse rate during the forty-five minutes following the injection.

Results

The resting cardiac output was 5.33 liters per minute, and, during exercise, it increased to 10.21 liters per minute, or almost twofold. Both the resting value and the amount of increase for the workload used were normal as judged by experience with the same test in normal subjects. The resting mean circulation time (19.7 seconds) and that during exercise (14.6 seconds) were also well within the normal range as determined by the method. Increase in pulse rate in response to the exercise, however, was distinctly less than normal. Changes in blood pressure, on the other hand, were almost identical in magnitude and sequence to those seen in comparable normal subjects.

Discussion

From the description of the operation, and from Mitchell's[8] description of vagal pathways to the heart, it seems highly probable that all connections between the left vagus nerves and the heart were severed. On the right, the lowest of the fibers passing from the vagus nerves to the heart were certainly interrupted, possibly leaving some of the upper and middle vagal cardiac branches intact. It is quite possible, however, that portions of those were also cut. At a minimum, it appears that perhaps three fourths of vagal efferent pathways to the heart were abolished. That the cardioinhibitory effect of the vagus nerve was markedly reduced, if not entirely abolished, is indicated by the persistently high pulse rate during the four months after operation. The fact that atropine in ordinary therapeutic dose did not increase the pulse rate also supports this view. In any event, the findings suggest that marked reduction in vagal influence on the heart by parasympathetic denervation in the human being results in a permanent increase in resting cardiac rate and, possibly, increase in blood pressure as well. On the other hand, it does not appear to deprive the organism of its capacity to make an effective circulatory adjustment to moderately heavy exercise. The patient described above was able to increase his cardiac output to a perfectly normal degree; much of the increase was clearly due to augmentation of the stroke volume, since his ability to increase his pulse rate during exercise seemed to be limited. In the normal, untrained person exercise presumably decreases vagal tone, with the result that the increase in pulse rate is relatively pronounced. Whether, during exercise in the normal subject, the increase in pulse rate is due to actual augmentation in sympathetic stimulation, on the one hand, or to sympathetic activity that is temporarily unopposed owing to decrease in tonic vagal effect, on the other, is not clear. Both effects, of course, may come into play simultaneously in the normal person during exercise. In the patient under discussion, some increase in sympathetic activity during exercise seems likely, since vagal tone was presumably markedly decreased at all times. The result supports Smithwick's conclusions about the role of sympathetic effects in the normal human adjustment to exer-

cise. The possibility that the increase in pulse rate in the patient described above was due to the direct myocardial effect of increased amounts of circulating epinephrine is, of course, not excluded. In any event our findings suggest that the patient possessed some nonvagal mechanism for increasing both pulse rate and cardiac output during exercise and that the importance of the vagus nerves in facilitating cardiovascular adjustment under these conditions may not be as great as is ordinarily supposed.

Summary

A case involving partial parasympathetic denervation of the heart in a human being is presented. In the resting state, the patient had a distinctly high pulse rate, and a further increase was noted during exercise. The exercise increment, however, was considerably less than that observed in normal subjects. The response of the cardiac output to exercise was normal. It is thought, in consequence, that the human being may possess important, nonvagal, mechanisms for adjusting cardiovascular function to exercise.

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THE CARDIOLOGIST LOOKS AT THE HAND*

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THE hand as a source of clinical information is so obvious that it may be neglected; yet there are no parts of the body more accessible for clinical study. Unique for its abundance of muscles, nerves and blood vessels, the hand is a powerful, dynamic organ capable of all kinds of reactions.

A physician first introduces himself as an examiner not only through the visual sense but also, very early, through the sense of touch. Thus, the greeting of a patient with a formal, though cordial, handshake can be highly informative: this is the first direct contact between physician and patient. The impression made at this time can be of prime importance. The flabby, cold, wet hand of the neurotic is unmistakable. In a subtle and efficient manner, the size of the patient's hand, its warmth, texture and type of response are immediately transmitted for evaluation. A handshake, incidentally, is a mutual response, and the information exchanged is reciprocal. A patient's confidence in a physician can be established quickly by a friendly but firm handshake.

It is the purpose of this paper to discuss the value of a simple examination of the hand for clinical information in cardiovascular problems. Despite the many technical advances achieved up to the present it is pertinent to emphasize time-honored diagnostic methods requiring only simple observation[1, 2] and no special apparatus.

In a general way the size of the hand is proportional to the rest of the body and a rough approximation of the cardiac silhouette may be obtained by examination of the size of the fist.[3] Under normal conditions the outline of the fist and the orthodiagraphic silhouette coincide, a small fist generally indicating a small heart.

One of the most striking findings in neurocirculatory asthenia is excessive palmar sweating.[4-6] Da Costa,[7] in his classic description of "irritable heart" in 1871, called particular attention to the changes in the hands: "there was also evidence of disorder of the sympathetic nervous system as shown in the itching of the skin and excessive perspiration from which many suffered." Sweating of the palms reflects emotional activities; it is increased during tension and excitement, but under ordinary conditions palmar sweating is not influenced by outside temperature.[8] Normal persons, particularly in a state of anticipation, demonstrate some degree of palmar sweating. Patients with neurocirculatory asthenia, however, are more likely to show this response more intensely and for a longer period. Dry palms in neurocirculatory asthenia constitute an anomaly.[4, 5]

The hands give other signs of an anxiety state. A tremor of large amplitude, for example, is commonly found in neurocirculatory asthenia.[9] A tremor, like palmar sweating, is a normal physiologic process. Under emotional influences it varies principally in amplitude, and this can be detected clinically. The combination of excessive palmar sweating and a pronounced tremor of the out-

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stretched fingers is a frequent finding in neurocirculatory asthenia and is almost never found in normal persons.[9, 10] In contrast to the warm, flushed hands of hyperthyroidism, those of patients with neurocirculatory asthenia are cold, cyanotic and mottled. These peripheral vascular changes are probably related to abnormalities in the capillaries.[11] Tobacco-stained fingers combined with short, chewed-off fingernails also stigmatize the neurotic. Tense persons are likely to have restless, fidgety hands, and this may be reflected in a characteristic handwriting.

Cyanosis and clubbing of the fingers have long been considered traditional signs of congenital heart disease. It is an interesting clinical fact that clubbing is never present at birth and is very rare before the age of two. In congenital heart disease when cyanosis is present it manifests itself before clubbing.[12] If clubbing is present without cyanosis in a child suspected of having congenital heart disease, a noncardiac explanation for the clubbing should be sought. Clubbing is generally proportional to the degree of cyanosis and reflects the degree of polycythemia.[13] For some unknown reason clubbing appears first in the index finger and thumb.[12]

When congenital heart disease is suspected, it is axiomatic to look for associated congenital anomalies. Thus, polydactyly and syndactyly may be associated with congenital heart disease. Arachnodactyly, a spiderlike deformity, characterized by abnormally long, slender fingers, was first described by Marfan[14] in 1896. This is a hereditary disorder in which there is a high incidence of cardiovascular anomalies — notably, septal defects, vascular hypoplasia and medionecrosis of the aorta, leading to dissecting aneurysm. Arachnoidactyly has also been reported in sickle-cell anemia, a condition easily confused with rheumatic fever.[15] It is interesting that long, slender fingers capable of hyperextensibility were recently observed in patients with neurofibromatosis associated with pheochromocytoma.[16]

Tuberous sclerosis of the brain (Bourneville's disease) is a rare, congenital and often familial condition in which a variety of neoplasms, including hypernephroma and rhabdomyoma of the heart have been described. In this disorder small, slowly growing para-ungual fibromas have been observed.[17]

The incidence of congenital heart disease in mongolism is high: close to 25 per cent.[18] The hand in mongolism is often distinctive, appearing fat and flabby. The fingers are short and cone shaped. The small finger often shows a curvature, and the second phalanx of the little finger is rudimentary. The thumb is shorter than usual. The back of the hand is generally soft and thin; the skin is wrinkled. In older patients, because of associated hypothyroidism, the skin appears dry and rough. Because of the poor circulation the hands in mongolism are usually cold and cyanotic. In a high percentage of cases the normal ridges across the palms present a characteristic pattern and a familiarity of the arrangement of these "lines" or palmar dermatoglyphics can be helpful in confirming the diagnosis of mongolism.[19]

There are few diseases in which the study of the hand is more rewarding than in subacute bacterial endocarditis. The diagnosis is occasionally established solely on the findings in the hand. A diagnostic sign of subacute bacterial endocarditis is the Osler node, first described by Mullen and later by Osler.[20] This consists of a small, raised, tender, red nodule the size of a pea, located in the pads of the fingers, in the thenar or hypothenar eminences and rarely on the sides of the fingers. This nodule lasts only a few days and, according to Libman,[21] is pathognomonic of subacute bacterial endocarditis.

The Osler node is sometimes confused with the Janeway lesion,[22] which consists of a small, erythematous patch located in the palm. In contrast to the Osler node, however, the Janeway lesion is never painful. The Janeway lesion is thought to be more characteristic of acute bacterial endocarditis but occasionally occurs in subacute cases.[23]

Trophic disturbances, petechial hemorrhages and embolic phenomena, common in subacute bacterial endocarditis, may be confined to the hand.[24] A distinctive hemorrhage beneath the nail is sometimes observed and has been designated a "splinter hemorrhage" because of its resemblance to a splinter.

A rare complication of subacute bacterial endocarditis is a ball-valve thrombus occluding the mitral orifice. In this condition patients may suddenly experience episodes of coldness, cyanosis and even gangrene of the fingers.[25] A ball-valve thrombus occluding the mitral orifice, however, is more likely to occur apart from subacute bacterial endocarditis than with it.

Despite the widespread use of antibiotics, clubbing of the fingers is still considered a hallmark of subacute bacterial endocarditis. It is an interesting clinical fact that with recovery clubbing of the fingers often recedes and may completely disappear.

Pallor is a more or less constant finding in subacute bacterial endocarditis. It is not sufficiently appreciated that a simple clinical method for estimating the degree of pallor exists in the observation of the color of the palms. According to Wintrobe[26] this site is more reliable for judging pallor than the mucous membranes or conjunctivas. Normally, the palms are pink. Early in anemia the palms appear pale, and as the anemia increases in severity the skin takes on a waxy, white look. In estimating the degree of anemia one should carefully observe the skin creases across the palm. It has been found that when the normal red color of this crease is lost the hemoglobin is usually below 7 gm. per 100 cc.[26] In aortic insufficiency, however, the palms tend to appear pale without the presence of any actual anemia.

Recognition of endocrine disturbances complicating cardiovascular disorders is of vital importance to the cardiologist. A clue to endocrine disturbances often exists in the hand. In hyperthyroidism the hands are tremulous, flushed, warm and moist. The skin is smooth and satiny. In hypothyroidism, on the other hand, the hands are dry, rough and cold; the palms appear sallow. A cretin's hand is characteristically underdeveloped. The hands in acromegaly are large, especially broad, and appear generally coarse and swollen. The fingers are relatively short, and the distal phalanges present a mushroomed, spade-like appearance. The skin and nails are overdeveloped. An occasional early manifestation of Addison's disease is hyperpigmentation about the knuckles; it is interesting that the hyperpigmentation seldom affects the palms, with the exception of the creases and folds. Small areas of intense pigmentation resembling freckles or molds may appear on the back of the hand, accompanied by yellowish discoloration of the nails.

An interesting and disabling complication of myocardial infarction is the shoulder-hand syndrome.[27, 28] This complication is characterized initially by a great deal of pain, stiffness and limitation of motion of the shoulder joint and girdle, usually the left, followed by involvement of the hands and fingers. The finger joints become stiff, swollen, painful and deformed. Trophic and vasomotor changes appear in the involved hands, especially the left. The skin is pink or red in the early stages and later cyanotic or pale. The involved hand, at a later stage, appears smooth, glossy and cold. Disturbances in the sweat mechanism are noted. In the advanced stage there is atrophy of the subcutaneous tissues and intrinsic muscles. Contraction and thickening of the palmar aponeurosis lead to a characteristic deformity, the so-called Dupuytren contracture.

Xanthomatosis is important to the cardiologist because of the high incidence of coronary-artery disease in this disorder. Cutaneous xanthomas occur over scattered areas of the body surface but are occasionally confined to the extensor surface of the wrist and hands, particularly near joints and tendons. Papular, tuberous or lobulated forms of xanthomas have been described.[17]

Gout is another metabolic disease of special interest to the cardiologist. Although infrequent, tophi may appear around the joints and tendons of the hands. Symmetric hyperkeratosis of the hands and palmar erythema have been observed in several cases of hyperuricemia.[29]

Alteration in the architecture and function of the liver may have serious circulatory repercussions. There are two signs of the hand suggesting disturbance in liver function — namely, erythema of the palms and spider angiomas.[30] Reddening of the palms, especially at the hypothenar eminences and fingertips is not pathognomonic of chronic liver disease; it has been observed in pregnancy, pulmonary tuberculosis, rheumatoid arthritis and deficiency states. Similarly, spider angiomas or pulsating vascular nevi are not pathognomonic of liver disease; they occur over the upper half of the body, being observed occasionally on the dorsum of the hand and rarely on the palms. Clubbing of the fingers has also been noted in cirrhosis of the liver.

In a recent informal review of the arterial spider and similar lesions Bean[31] presented striking photographs of vascular skin lesions in the palms and fingers of patients with Osler's disease or hereditary hemorrhagic telangiectasia. It is important to recognize this disorder, which may be the basis of unexplained hemorrhage from various sites. It may be associated with an arteriovenous fistula of the lung.[32] Classically, patients with arteriovenous fistula demonstrate a diagnostic triad of cyanosis, clubbing of the fingers and polycythemia.

A host of deficiency states may be encountered in patients with long-standing cardiac disorders. In a typical niacin-deficiency state the skin changes in the hands are often distinctive. Pellagra erythema is an early sign, confined chiefly to the dorsum of the hand and rarely extending higher than the wrist line. In the advanced stage of pellagra the skin of the hands is thin, atrophic and often complicated by secondary infection. Subungual bleeding may be a manifestation of scurvy. In severe malnutrition, the fingernails appear dull, dry and brittle and are often studded with pits and ridges. Urbach and LeWinn[33] have described white cross striations in the nails of a patient suffering from a coronary occlusion. Similarly, the pocking or stippling of the nails that Rosenau[34] (1922) found in 95 per cent of all cases of rheumatic fever and chorea is probably on a nonspecific nutritional basis.

Raynaud's syndrome is a peripheral vascular disorder of unknown origin primarily involving the fingers. It should be pointed out, however, that the syndrome may be secondary to a wide number of conditions, such as lupus erythematosus, dermatomyositis, scleroderma and pressure from a cervical rib, tumor or aneurysm encroaching on the brachial plexus.[35, 36] By way of contrast, an interesting disorder is erythromelalgia (erythermalgia), in which the hands are characteristically swollen, red and warm. Erythromelalgia also occurs as a secondary manifestation to a number of conditions, such as hypertension, polycythemia vera, diabetes mellitus, gout, rheumatoid arthritis, arteriosclerosis obliterans and thromboangiitis obliterans.[37]

The hands are frequently involved in the diffuse collagen diseases. Frank arthopathies with rheumatoid-like features in the finger joints may occur.[38] In disseminated lupus erythematosus characteristic erythematous lesions about the fingernails and the thenar and hypothenar eminences have been described.[39] The hardened, smooth, wrinkleless appearance of the skin of the hand in scleroderma is

striking; in advanced scleroderma the claw hand is diagnostic. Mention should be made of the subcutaneous nodule in active rheumatic fever. This nodule is apt to appear over bony eminences but may be confined to the knuckles.

Involvement of cardiac musculature occurs in certain types of muscular dystrophy, one of the earliest manifestations of which may be atrophy of the intrinsic muscles of the hand. Similarly, in diphtheria weakness and paralysis of the extensor muscles of the wrist, with a characteristic wrist drop, may be encountered.

In advanced congestive heart failure the hands are invariably cold; the veins on the dorsum are engorged, and the fingernail-bed cyanotic. Hyperpigmentation of the dorsum of the hands and fingers has been noted in some children with congestive heart failure. This pigment is hemosiderin.[17]

In the past a great deal of attention was given to capillary pulsation (Quincke pulse), demonstrated in the nail bed or skin at the root of the nail in patients with aortic insufficiency. The Quincke pulse, however, is not pathognomonic of aortic insufficiency; it has been described in fever, anemia, hyperthyroidism and patent ductus arteriosus. More important, the hands are admirably suited for study of the dynamics of the peripheral circulation.[40, 41] As a matter of practical importance, the color and temperature of the skin of the hands may yield more information of impending shock than the pulse or blood pressure. Indeed, a warm, pale hand abruptly changing during the course of an illness to a cold, deeply colored cyanotic appearance is dramatic evidence of peripheral circulatory failure.

Summary

The human hand is a unique organ in which an extraordinary amount of clinical information is available. A number of conditions are discussed in which a simple examination of the hand discloses interesting and, at times, revealing information in cardiovascular problems.

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MEDICAL PROGRESS

FOOD POISONING (Concluded)

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OTHER BACTERIAL GASTROENTERITIDES

Contamination with *Esch. coli*, *P. vulgaris*, *A. aerogenes* or *Cl. perfringens*, organisms ordinarily considered nonpathogenic by the oral route, has been implicated in food-poisoning outbreaks. The rate rarely exceeds 2 or 3 per cent of the annual total cases of food poisoning, but the outbreaks may involve large numbers of victims. No particular food seems to be responsible, nor do the outbreaks follow a seasonal pattern. With few exceptions the true etiologic significance of the bacteria incriminated has never been satisfactorily proved. Dack[12] has dealt with this problem fully, so that attention is called only to selected old and more recent aspects of general interest.

Dolman[13] made several feeding experiments on volunteers using filtrates prepared from a hemolytic coliform bacillus, a hemolytic enterococcus and three proteus strains. None produced significant reactions when taken by mouth. To test the possibility of a nonfiltrable infective factor in food heavily contaminated, volunteers were given meat pies artificially infected with cultures suspected of causing food poisoning. The number of *P. vulgaris* or *Esch. coli* was much higher than that originally reported for the implicated foods, and the volunteers in all probability consumed numbers of organisms far in excess of the number unwittingly consumed by the victims in the various food-poisoning episodes. No ill effects followed the consumption of the pies. Although a larger number of feeding experiments with strains freshly isolated from suspected foods must be carried out before these bacteria can be exonerated, "there is at present no significant evidence pointing to such a role."[13]

This conclusion now deserves revision, particularly in view of recent experiments in feeding adult volunteers with definitely identified coliform organisms, *Esch. coli 55*, B_1 or *111*, B_4, which had been isolated from hospital outbreaks of infant diarrhea. On ingestion of 143,000,000 to 1,725,000,000 organisms, several adults manifested a gastroenteritis similar to food poisoning. All cases that exhibited symptoms, with two exceptions, showed an agglutinin rise. The severity of symptoms corresponded roughly to the dosage fed.[125, 126] There is now ample proof that certain strains of the *Esch. coli* group, when present in large numbers in food, may act as the inciting agent of gastroenteritis. Serologic identification of the coliform organisms will greatly assist — and in fact will be the determining factor — in proving the etiologic relation to gastroenteritis.

In another experiment on volunteers, Dolman[13] tested his hypothesis that food-poisoning outbreaks, frequently reported as of unknown origin, are due to enterotoxigenic staphylococci, which may be masked, overgrown or even extinct when the incriminated food reaches the laboratory. Three persons were made violently ill by consuming the saline extract of a sausage inoculated with enterotoxigenic staphylococci and subsequently with *P. vulgaris*. At the time the sausages were toxic, staphylococci could not be detected. Sausages inoculated with *P. vulgaris* alone were eaten without ill effects. These experiments, not generally known, have a significant bearing on the interpretation of some laboratory reports on which the etiologic classification of food poisoning is based.

Occasionally, particularly in the older reports, the significance of staphylococci present in chocolate éclairs was not appreciated because the strain failed to cause symptoms when fed to animals; however, an organism belonging to the aerobacter group produced metabolic products toxic to certain animals.[125] This type of evidence has been amply discredited because filtrates of the common intestinal bacteria when injected into animals may be toxic, but without effect when orally administered to man. The claim that *paracolon* or *aerogenes* is responsible for outbreaks is faithfully perpetuated in health-department reports without convincing bacteriologic proof or feeding experiments on human volunteers.

A group of organisms frequently present in food served in warm countries and recently studied in connection with 30 outbreaks in Egypt,[126] *Pseudomonas pyocyanea*, deserve some attention. Preliminary feeding experiments on kittens with heat-killed cultures in milk indicate that this pigmented bacillus produces a powerful toxin. Volunteer tests are urgently needed.

Anaerobic bacteria, particularly *Cl. perfringens* (*w.lchii*), have been implicated in several outbreaks in the United States, in England and in Sweden. Creamed-chicken croquettes contaminated with these organisms caused gastroenteritis after an incubation period of eight to twelve hours in the original outbreak and in a volunteer who ingested food artificially contaminated with the *Cl. per-*

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fringens isolated from the croquettes.[127] In 24 outbreaks in England there was evidence that the cause was *Cl. perfringens*.[11] It was associated with made-up meat dishes in 22, with potato crisps in 1 and with jam in 1. On bacteriologic investigation of food products suspected of having caused food poisoning, Österling[128] found *Cl. perfringens* to be the predominant micro-organism in 15 of 33 outbreaks. These were characterized by an average incubation period of ten to twelve hours, diarrhea, abdominal pains, rarely vomiting and a duration of not more than twenty-four hours. In 7 of these outbreaks Österling established the pathogenic role of this anaerobe by infecting corresponding foods with the isolated strains and then administering the food to volunteers. These tests furnish some evidence that certain strains of *Cl. perfringens*, a common saprophyte and intestinal parasite in man and animals, may, under conditions not yet clarified, play a considerable part in the mild food-poisoning outbreaks common in Scandinavian countries.

How decisive volunteer experiments may prove is well illustrated by two recent reports from Norway[129] and Denmark.[130] Four large outbreaks, involving over 600 persons, occurred in institutions in Norway. In one episode, 129 of 184 persons, eight to twelve hours after a Sunday midday meal including custard prepared on the previous day, suddenly had nausea, pain in the lower abdomen, tenesmus and diarrhea, with a normal temperature. Recovery was uneventful, with not much exhaustion, after six to twelve hours of illness. The tested custard contained 100,000,000 gram-positive, spore-bearing *B. cereus* per cubic centimeter. The spores were found in large numbers in the custard powder and were apparently derived from the corn powder used in its preparation. The organism was not present in the feces in any great number. Hauge,[129] a competent food bacteriologist, believes that the symptoms were caused by a toxin. The typical disease was reproduced in 4 of 6 volunteers who ate custard inoculated with *B. cereus* and left at room temperature. Several smaller outbreaks are also mentioned, one caused by cod-liver capsules. The gelatin capsules contained *B. cereus* in large numbers.

The Danish report[130] of an outbreak in a summer camp confirms the findings of Hauge. Fifteen of 18 adults and 106 of 130 children between the ages of eight and sixteen fell ill after eating a yellow pudding made the day before and kept at room temperature (favorable to growth of this organism). *B. cereus* was isolated in pure culture from the pudding. Examination of other foods eaten at the same meal revealed no pathogenic organisms. The water and the milk supply of the camp were exonerated. Though the powder from which the pudding was prepared had been used up, indirect evidence strongly incriminates *B. cereus*. The isolated organism, widely distributed in soil, dust, plants and elsewhere, produced beta hemolysis and a positive Voges-Proskauer reaction.

These observations convincingly show that some normally nonpathogenic organisms, perhaps specific types, may cause poisoning when present in massive numbers in food. The experiments on volunteers, not animals, confirmed the enterotoxigenic properties of the organism suspected.

Food Poisoning with Involvement of the Central Nervous System

Botulism

This is a specific intoxication with the toxins of *Cl. botulinum* or *parabotulinum*. The five serotypes, A, B, C, D and E, exist in nature as sporulating saprophytes and grow freely in a great variety of inadequately preserved animal or plant foods. During resultant spoilage a powerful toxin is formed and, on ingestion, is absorbed, ultimately inducing some changes in the motor-nerve terminals at the neuromuscular junction; acetylcholine output is diminished, with effects resembling denervation.[131] The name botulism (from *botulus*, sausage) has, at least in the United States, lost its significance, since animal products play a subordinate role here. Most outbreaks are caused by inadequately preserved, understerilized plant products. The classic textbooks on food poisoning[3, 4, 12] and the monographs by Dickson[132, 133] and Meyer[134] thoroughly describe this interesting disease.

Prevalence. Although botulism is subordinate in the annual lists of food-poisoning outbreaks, one would expect that the deaths would attract enough attention to assure fairly complete reporting. They do not. The summary of food-borne outbreaks due to foods other than milk and milk products reported in the United States for 1938 to 1951 lists 99 outbreaks, whereas replies to questionnaires sent by the Hooper Foundation to state health departments described almost twice that number, 187. In all probability, again, only outbreaks, not single cases, are adequately reported. As a measure of the relative importance of botulism in the United States, the histories and data collected by the Hooper Foundation are compared and discussed. The 500 single or group intoxications in the United States from 1899 to December, 1952, involved a total of 1324 persons, of whom 846 died. The mortality rate, which has at times reached 67 per cent, has dropped only to 62 per cent. Between 1931 and 1947 the annual number of single or group intoxications was, as a rule, above 10; in 1935 it reached 26. Between 1948 and 1952, 6 to 8 outbreaks were placed on record every year. The increased preserving activities incident to the depression and to World War II may have been responsible for the higher annual incidence in 1935 and 1944. On the other hand, through education of the housewife during the war, the old methods of

home canning have been largely replaced by safer procedures.

For the whole period three western states — California, Washington and Colorado — had over 50 per cent (289 single cases or outbreaks) of the total reported. Next in frequency were New York, New Mexico and Montana. Every state has reported 1 to 10 outbreaks.

Dolman,[135] in a review of botulism in Canada, records 10 known occurrences, involving 56 persons, with 31 deaths (55 per cent). Only 4 of the episodes were proved bacteriologically.

Source. In the United States, understerilized or inadequately preserved vegetables are the most frequent sources. The histories of the 500 single or group intoxications list the foods involved as follows: string beans (101), corn (52), beets (25), asparagus (25), spinach or chard (24), chili peppers (16), olives (14), peas (12), figs (11), mushrooms (10), tomatoes (1), apricots (4), pears (3), meat products (38), fish or seafood (30), milk or milk products (7). A great many other plant and animal foods have been incriminated. In fact, no product, if not acid (pH below 4.5) and free from mold and yeast or other microbes in the canned content, is immune to botulinus spoilage.[136] In 49 intoxications the causative food was unknown; the symptoms were typical.

Up to 1925, commercially canned foods manufactured in the United States had been at fault in 32 cases, but intensive research, supported by the protective measures originally devised by the State of California, led to the adoption of scientific procedures by the canning industry.[137] Hence in the United States during the past twenty-eight years, intoxications following consumption of commercially canned foods have been rare and have been due largely to foreign commercially preserved fish products (sprats, antipasto and clams) or food specialties (muscari, shallots). From the standpoint of botulism, food commercially canned in the United States is the safest.

Recently, a single intoxication after the consumption of commercially prepared spread cheese known as "Liederkranz type" attracted attention.[138] Early concern that this type of food might be a hazard has been dispelled by the recognition that though raw milk is quite often contaminated with the spore of *Cl. parabotulinum* and other anaerobes and the final cheese products may still contain viable spores, toxins cannot be found. The factors responsible for the inhibition are not understood; they must be most effective because most extensive examinations of many thousands of packages of this and similar types of cheese have revealed only one toxic cheese. This was the one responsible for a fatal case of botulism in a fifty-three-year-old man.

A final comment on the causative foods: in about 10 per cent of the listed botulism intoxications the causative food was not available. Bacteriologic proof — finding the toxin or the anaerobes responsible for the spoilage — was furnished in only 162, or slightly less than a third of the clinically recognized episodes. Several days usually elapse between the consumption of the toxic food and the investigation. By that time the food has been consumed, discarded or destroyed, or under fortunate circumstances it has been fed to chickens. The crop content of a fowl dead from limberneck may furnish a clue to the food involved and it may also provide specimens for bacteriologic examinations. Even in California, with epidemiologic intelligence services alert to botulism, it has been impossible to prove in 62 (31 per cent) of 190 outbreaks the presence of the causal toxin or agent in the food.

Distribution and importance of different types of Cl. botulinum. The cause of botulism is the toxin produced by a variety of large, motile, gram-positive spore-bearing anaerobic bacilli, widely distributed in soil. The spore of some strains of the proteolytic *Cl. parabotulinum* are resistant to boiling water, even for three to six hours. The original strain isolated by van Ermengem from a ham, Type B, is considerably less resistant and shares this property with all the nonproteolytic strains, *Cl. botulinum*. The antigenicity of the toxin is type specific. Type C is again subdivided into alpha and beta. These subtypes share with Types D and E and one European Type B the property of being non-proteolytic.

Cl. parabotulinum A and B are commonly encountered in America, and *Cl. botulinum* C and E, less frequently. Type D has been isolated only in South Africa. Until recently human intoxications from Type C or D toxins were not recognized. In October, 1950, the stomach content in the only fatal case of clinical botulism in a family group of 4 with a confused history regarding the actual food consumed produced symptoms of botulism in mice. The heat-labile toxin was not neutralized by the commercial or experimental antitoxins on hand at the Hooper Foundation. However, the anaerobe isolated from the stomach content of the patient was Type C alpha. In the dose of 1500 mouse M.L.D. (minimum lethal doses) it proved fatal to 1 monkey. In another monkey, 2000 mouse M.L.D. administered by stomach tube produced severe classic symptoms, followed by slow recovery, whereas 1000 M.L.D. induced mild transient illness. Doses of more than 4000 M.L.D. given orally were invariably fatal. This is decisive evidence that the toxin of probably all known Type C beta strains is pathogenic for man.[139]

In the intoxication following ingestion of cheese there is evidence that 3500 mouse M.L.D. of type B toxin invoked the symptoms within seven hours and death fifty-seven hours after the cheese was eaten. It is probably correct that the mere tasting of a pod of spoiled string beans might cause fatal intoxi-

cation. A few hundred mouse M.L.D. of toxin can cause botulism in human beings.[138]

In 2 outbreaks (28 cases) in Australia the diagnosis rested on clinical evidence entirely. The common item in the meals in both outbreaks was canned beetroot, but none were available for examination. In 1 outbreak an unsound, punctured can of beetroot found in the garbage pit yielded *Cl. botulinum*, Type B.[140]

Since the original identification of Type E, isolated by Russian workers from the intestines or muscles of sturgeons, at least 3 outbreaks in the United States, 3 in Canada, 1 in Alaska, 1 in Japan (24 cases, 4 deaths) and 1, possibly, 2 in France have been proved as Type E botulinus intoxication.[135, 139, 140-146] The foods were commercially canned (2 cases) or home-canned (3 cases) fish, smoked fish (1 case), uncooked beluga (white-whale) flippers (5 cases), pickled herring (24 cases) and commercially prepared mushroom sauce (3 cases). Association of Type E with fish is further exemplified in the isolation of this type from the intestinal content of a perch in France.[147] Knowledge of Type E has been greatly fostered by Dolman, who was the first to demonstrate the organism in soil, from a chicken run in Vancouver, British Columbia.

The distribution of the different types of *Cl. botulinum* in soil in the United States is interesting. Type A is the most prominent type in the West, Type B being slightly more frequently found in the East. In 162 outbreaks in the United States, Type A was responsible in 126, Type B in 32, Type E in 3, and Type C in 1. In 2 outbreaks in which a mixture of Types A and B was found in the food, the former was probably the deadly toxin. The outbreaks are listed as due to Type A because they occurred in the West. The isolation of certain types from food convincingly reflects the geographic distribution of *Cl. botulinum* in soil throughout the country. In California, with 61 proved botulism intoxications due to locally grown products, 4 were Type B and 1 Type E; in Washington, with 17 outbreaks, 15 were Type A and 2 were Type B; in Colorado, with 9 outbreaks, 1 was Type B; in Oregon all of 8 outbreaks were type A; in New York 7 of 9 outbreaks were Type B and 2 Type E; in Tennessee, with 3 outbreaks, 1 was Type B. In Kentucky, Maryland and Virginia only Type B has been isolated from incriminated food. Nowhere in nature can soil be considered free of the spores of *Cl. botulinum*, of potential hazard to human beings.

A recent review by Fahraeus[148] of the distribution in Europe again calls attention to the predominance of the proteolytic (*Cl. parabotulinum*) and nonproteolytic (*Cl. botulinum*) Type B strains there. The isolation of Type A from ooze of a lake in Sweden and the previous demonstration of the same type in a soil specimen from Scotland settle two moot aspects of the botulism problem in Europe. Except for one specimen of soil from the grounds of a riding academy in Zurich that contained it, Type A had rarely been found in Europe. It was found in several foods: canned beef and ham in Switzerland,[149] and preserved rabbit meat, fish and soup prepared from tuna fish in France.[150] No definite conclusion can be drawn about the distribution of nonproteolytic Type B, which, since the days of van Ermengem, has frequently been isolated from animal and fish products preserved in Europe — in Belgium, in England (in pickled herring), in Germany and in Denmark. Nor is anything known about the distribution of Type C recently associated with equine botulism in Belgium,[151] France[152] and Spain.[153]

The recent observations merely continue to lend support to long-known facts — *Cl. botulinum* and *parabotulinum* have a world-wide ubiquitous distribution. Wherever and whenever food is even slightly contaminated with soil and then inadequately preserved or underprocessed in hermetically sealed containers it may become botulinogenic.

The toxin and pathogenesis of the intoxication. The toxins of *Cl. parabotulinum*, Types A and B, have been purified as simple proteins. Type A has been crystallized and fully characterized.[154-156] Cultures of Type A contain hemagglutinins, not identical with hemagglutinating activities.[157, 158] The antigens are either different chemical groupings on the same molecule or two entirely different and separate entities.[159] The action of concentrated Type A toxin is not reduced by pepsin as might be expected in view of its pathogenicity by the oral route.[160]

Several studies deal with mass production of toxins,[161] the preparation of toxoids and the antigenic response of man.[162] The resistance conferred by toxoid may be a tissue immunity that renders the motor-nerve terminals highly resistant to the toxin. Always of considerable practical importance are observations on the thermal destruction of the toxins in canned foods, particularly vegetables. Type A toxin, a globulin with an iso-electric point close to pH 5.6, loses its toxicity through denaturation. The rate of destruction at 75° to 80°C. is slowest at about pH 5.0 in vegetable liquor and at a reaction slightly closer to the iso-electric point in cooked meat liquor. At pH 7.5 the toxin loses 100,000 M.L.D. in ten minutes at room temperature. The effect of pH on Type B toxin is less marked; in a range of 4.5 to 7.0 this toxin appears to be more readily destroyed than Type A. This apparently greater lability may be masked by the well known fact that mice and rats are less susceptible to Type B toxin[121, 155] and that, in view of the uncertain kinetics of the reaction, the true differences in the heat resistance of the two toxins may be less than the reported experiments indicate.[163, 164] The conditions of destruction of botulinum toxin are not simple functions of time and temperature unless toxin is heated in a specific

ionic and chemical environment. All Type A broth toxins are destroyed at pH 5.0 at 80°C.

In a definition of safe methods of detoxifying foods suspected of containing toxins it is most important to insist that all parts of the food be heated to at least 80°C. and to recommend a liberal safety factor in the procedure. Boiling home-canned food suspected of being inadequately processed for at least ten to fifteen minutes has proved adequate in a number of outbreaks. The boiled food failed to cause botulism, but the housewife who tasted it before cooking it died of botulism. Apparently edible string beans may emanate an abnormal odor when heated and thus warn the prospective consumer that they may be botulinogenic, but not all toxin-ridden foods provide such warning. Toxin may form rapidly in preserved food,[165] as a recent report from Kiel confirms. Botulism developed fifteen hours after the patient ate herring preserved in vinegar for only four days.[166]

The work done hitherto on the action of botulinus toxin strongly suggests that it acts by inducing some functional derangement of cholinergic nerve fibers, probably at their secretory endings, giving effects resembling denervation.[167] By an irreversible fixation of the toxin to the fine nerve fibers, transmission of the impulse is abolished and acetylcholine is not released, resulting in observed neuromuscular block. Through experiments on the effect of intraocular administration of Type A toxin to rabbits and through electrophysiologic studies it has since been concluded that the toxin does not interfere with the process of nerve conduction. The action is specific on autonomic nerve fibers of the cholinergic type.[168-170] The poisoned phrenic nerve fails to release acetylcholine.[121] All postganglionic fibers, irrespective of their origin or myelination, if they are cholinergic are paralyzed by the toxin. On further analysis of myenteric plexus fiber preparation the toxin did not paralyze to such an extent that this plexus would cease to respond to nicotine stimulation of the ganglion cells. In fact, the action was the opposite — stimulation of ganglion cells that are inhibitory and appear to be the cell bodies of short adrenergic neurones, apparently capable of resisting large amounts of toxin. The unstable blocking of nerve impulses was responsible for the conclusion that the toxin does not produce true paralysis. The preganglionic fibers of the ciliary ganglions are paralyzed by retrobulbar injection of toxin, and this paralysis leads to constriction of the pupil. Many of the classic symptoms of botulism and the lack of reversal by antitoxin have been made more readily understandable by the careful physiologic studies of Burgen and his associates[121] and by Ambache.[168-170]

Botulism is usually considered an intoxication that follows the ingestion of a preformed toxin in inadequately preserved food, but now in rapid succession the American medical literature presents reports of 3 fatal wound infections in which *Cl. parabotulinum* was isolated.[171-173] The unsolved problem of the toxico-infective character of botulism is thus reopened.[138]

Clinical manifestations and treatment. The onset in human beings may be one of two kinds: initial gastrointestinal disturbance followed by the typical botulism symptoms or initial typical symptoms. The acute gastroenteritis apparently results from local irritation by bacterial metabolites similar to that produced by other anaerobes — for example, *Cl. perfringens* — in spoiled food. This has occurred in about a third of the recorded cases in the United States. The nausea, vomiting and diarrhea begin early, last for twelve to thirty-six hours and disappear with the onset of the typical nervous-system involvement. The typical onset is twelve to thirty-six hours, usually less than forty-eight hours, after ingestion of toxic food. An early onset, in two to four hours, is invariably accompanied by gastrointestinal symptoms. Onset has been delayed as long as the eighth, ninth and fourteenth days.

Descriptions of the principal symptoms — extreme weakness, dryness of the mucosa, loss of accommodation, ophthalmoplegia and dysphagia — have been amplified in some of the recently reported histories. Laryngeal spasms, tonic convulsions in the limb muscles with the hands in tetany and shock with low blood pressure and rapid pulse have been noted. The possible direct action of the toxin on the cardiovascular system is repeatedly emphasized.[174-176] Attention has been called to the slightly reduced serum potassium level during the first seven days of illness and to temporary depression of the T waves on the electrocardiogram.

Prevention is, of course, the best treatment. Once typical symptoms have appeared the chances for recovery are not at all favorable — about 1:2. Physiologic experiments have shown that only massive amounts of antiserum can exert an antagonistic effect on the toxin, which is anchored to the motor-nerve terminals. Through the years evidence has accumulated in the international literature that use of type-specific antitoxic serums in large doses will save lives. Every patient should have the benefit of early treatment with bivalent (Types A and B) antitoxic serum in the dose of not less than 10,000 units every eighteen to twenty-four hours. It should be liberally diluted with a 5 to 10 per cent solution of dextrose and injected intravenously. As soon as the type has been determined, particularly if Type E is responsible, monovalent serum should be injected.[177] In addition to treatment with antitoxin and possibly antibiotics to prevent secondary complications, recent reports demand that efforts be made to combat shock with blood transfusions and dextran.[175]

Shellfish Poisoning

Shellfish have been responsible for many outbreaks of typhoid fever, but seem to have caused relatively few paratyphoid or other salmonella infections. In the master lists for 1945 on food poisoning in the United States, for example, only 3 outbreaks of typhoid fever were attributed to clams, and 1 to oysters. Outbreaks of gastroenteritis attributed to the consumption of raw or cooked shellfish, cockles and oysters are occasionally the subject of official reports. The outbreaks are rarely investigated, so that the cause usually remains unknown. Examination of mussels in certain coast areas of England has disclosed the presence of *S. brancaster, typhimurium* and *newport*, but the number of pathogens was very small.[178] With the increasing use of shellfish by man as food there may be more opportunities for him to become infected from this source.

It is gratifying to read an account elucidating some of the circumstances leading to the unwholesomeness of this food: the description of an outbreak of 437 cases at Southend on Sea in England during a period of sustained abnormally high temperatures in September, 1949.[179, 180] Detailed descriptions of symptomatology in 84 cases stressed the fact that vomiting, diarrhea and griping pain may be most severe in the aged. Most of the illnesses were trivial, and recovery was quick. Bacteriologic examinations disclosed no recognized pathogen, though the nonspecific bacterial count of many of the mollusks tested was high. Although cooking had effectively sterilized the shellfish, they were proved to have been subsequently contaminated through careless handling. During the unusual weather and temperature minor contaminations were followed by bacterial growth of such magnitude that many of those who ate the shellfish became ill. Raw and cooked shellfish held under poor hygienic conditions furnish an excellent environment for nonspecific massive bacterial growth and a certain degree of spoilage. The responsibility of the cockles became apparent through the extent of the outbreak; single cases doubtless escaped detection, although favorable conditions for recognizing them after the publicity prevailed over wide areas and the episodes had repeated themselves for several years. Improvement in technics and extended use of refrigeration have largely eliminated this form of nonspecific food poisoning.

A second type of shellfish poisoning, recognized since 1793, the paralytic form, is conclusively associated with a specific poison readily extractable from the bacteriologically clean mussel. Gastrointestinal symptoms in man are quite variable and subordinate to the paresthesias and paralysis that may appear within ten minutes of the ingestion of the offending shellfish or broth prepared from them. Tingling numbness around the lips is followed by prickly feelings in the fingertips. Ataxia and giddiness soon appear. The staggering and drowsiness have been likened to the early stages of drunkenness. Mental symptoms vary; most patients appear calm. Dryness and gripping sensations of the throat are among the complaints. Incoherence of speech is quite common, and complete aphasia has been reported. As a rule the reflexes are not affected. There is nothing characteristic of the heart rate. Death from respiratory failure occurs quickly, but as a rule if the patient survives for twelve hours the prognosis is excellent. Autopsy reveals no significant findings; the nerve cells are not altered. Several people have had a second attack of mussel poisoning a few years after the first. Prompt evacuation of the gastrointestinal tract with apomorphine is considered more effective than gastric lavage or purging. To enhance excretion, diuresis may be attempted with 5 per cent ammonium chloride intravenously. Artificial respiration must be given if respiratory embarrassment ensues. Shock may require treatment. Neither digitalis nor alcohol should be given.

Since 1927 the Hooper Foundation has collected the histories of 409 cases of mussel or clam poisoning. There have been 35 deaths (8.5 per cent). Most of these poisonings occurred at irregular intervals of several years along the central California coast, with a sprinkling of extensive outbreaks from Juneau, Alaska, to southern California and the Gulf of Mexico. All cases occurred between May 15 and October 26.

Medcof and his associates[181] and Needler[182] reported a total of 21 cases of paralytic poisoning due to the soft-shell clam *Mya* in the areas of the Bay of Fundy, New Brunswick and Nova Scotia. Several cases attributed to ingestion of the white mussel (*Donax serra*) or of the black mussel (*Mytilus edulis*) have been observed near Cape Town, South Africa.[183, 184] There were 12 cases, with 4 deaths, due to these shellfish in Belgium.[185] Mussel poisoning has also occurred in New Zealand.[186] Before 1915 Germany, England, Ireland and France had reported, over a period of twenty years, approximately 110 cases.[187] The world-wide distribution of shellfish poisoning is geographically and chronologically illustrated in Figure 1.

Some dangerous shellfish along the American coasts and on the American continents have been identified and are, in descending order of importance, the California mussel (*Mytilus californianus* and *edulis*), the soft-shell clam (*Mya arenaria*), the butter clam (*Saxidomus*), the white mussel (*Donax serra*) and the red or horse mussel (*Modiola modiolus*). Other potentially poisonous shellfish, though toxic in varying degrees, have not been incriminated in poisoning cases: the bar clam (*Mactra solidissima solidissima*),[188] the razor clam (*Eusis directus*) and the sea scallop (*Pecten grandis*).[184] The butter clam plays a role in the areas of Alaska and British

Columbia, areas from which canned shellfish are shipped.

Through the brilliant studies of the late Hermann Sommer and his group it was learned that the poisonous properties of mussels are derived from plankton ingested by the mussels. The paralytic poison has been extracted from plankton samples collected during the summer, and the amounts of the poison were roughly proportional to the number of dinoflagellate plankton, *Gonyaulax catenella*. Cultures in relatively simple sea-water mediums yield excellent growth of this dinoflagellate, and on the average, 3000 organisms yield 1 mouse unit of the poison defined below.

All basic studies on mussel poisoning on the Pacific Coast have been focussed on *Gonyaulax catenella*. *Gonyaulax tamarensis*, on which shellfish feed in the Bay of Fundy, is also poisonous,[181, 182] and other species of dinoflagellate are suspected of carrying the poison.[189] *Gonyaulax tamarensis* is the only other plankton observed whose periodic seasonal increases in number coincide with the appearance of high toxicities in shellfish well studied on the Pacific Coast.[190]

The free-swimming, dark-orange dinoflagellate, *Gonyaulax catenella*, multiplies by photosynthesis, forming an aggregate of chainlets counting 2 to 12 individuals. The deep-rust-colored luminescent appearance of ocean water during midsummer reflects the abundant multiplication of these plant cells, a fact realized long ago by the Poma Indians. It warns that any plankton feeder may be highly poisonous. These grossly visible signs of dinoflagellate multiplication may not be apparent. It is therefore necessary to advise against eating shellfish during the months of May through October, to post appropriate warnings along the beaches where they might be collected and to carry out thorough shellfish quarantine procedures.[191]

To give a basis for comparison, the method of preparing the material for estimating the toxicity and the terms generally used will be described. A mouse unit is the amount of poison that will kill a 20-gm. mouse in fifteen minutes after intraperitoneal inoculation. To gauge the toxicity of shellfish, Sommer and his group weighed 3 mussels, selecting those that weighed approximately 50 gm. each, and removed the livers. To the liver of each 50 gm. mussel is added 10 cc. of one-tenth normal hydrochloric acid. The mixture of three livers is boiled for ten minutes and then centrifuged. The supernatant is injected intraperitoneally into mice. If a 20-gm. mouse dies within fifteen minutes of receiving 1 cc. of the cleared extract, the concentration of poison is expressed as 10 mouse units per 50 gm. of mussel.

The Canadian workers,[181] sampling larger shellfish, extracted 100 gm. of whole minced shellfish meat with 100 cc. of one-tenth normal hydrochloric acid and tested the supernatant on mice by the intraperitoneal route. If 1 cc. proved fatal to the animal in fifteen minutes the poison concentration was

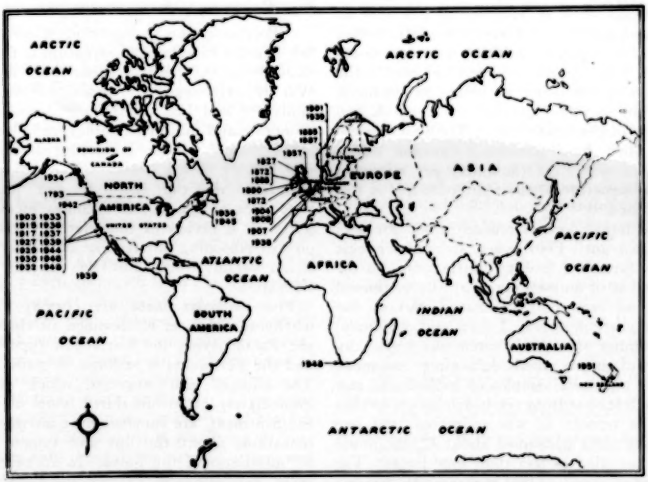

FIGURE 1. *Reported Cases of Shellfish Poisoning.*

considered 200 mouse units, the toxicity level. For comparison with the Sommer standard of mouse units per 50 gm. of mussel, the Canadian units must be divided by 7. Repeated tests have shown that 30 per cent of the total weight of the shellfish is meat. Thus, 100 gm. of meat, as used by the Canadians, is equal to 350 gm. of total weight, or equal to 7 shellfish weighing 50 gm. each. A toxicity level of 32,000 mouse units by the Canadian method is the equivalent of 4500 mouse units per 50 gm. of mussel by the Sommer standard. It would be advantageous if the same unit, preferably the Sommer standard, were used to express toxicity.

The poison is one of the most potent known for mammals and birds. It surpasses any other known alkaloid, of which it is one. Readily soluble in water and alcohol, insoluble in ether and chloroform, it loses its stability, but not necessarily its toxicity, in aqueous solution with an increase in pH and an increase in temperature. It exerts a powerful action on the respiratory, cardioinhibitory and vasomotor centers.[192, 193] Considerable progress has been made in purification by use of ion exchange on synthetic zeolite, and by chromatography on Norit A and crystallization of the helianthate. The purest preparation obtained from poisonous mussels has a toxicity of 4 mouse units (Sommer) per microgm. The chemical structure of the toxic principle is still to be determined.[194-197]

The actual lethal dose of mussel poison for man was not known until 1946, when an epidemiologic investigation furnished leading information. In the past the number of mussels eaten by the victims of the poison had been only estimated, but in one episode that year, involving 2 men and a woman, the exact number of mussels eaten was known by the number of empty shells left after the meal. Furthermore, adequate samples of cooked and raw mussels were left over from the beach picnic so that they could be tested. It was estimated that one member of the party consumed about 42,000 mouse units; this man died in less than four hours. The woman ingested about 22,000 mouse units, became seriously ill and was put in a respirator for four and a half hours. This supportive measure was probably responsible for her recovery. The second man, who had eaten mussels containing about 17,000 units, had mild symptoms and recovered. If this is an accurate estimate, the M.L.D. for man is probably between 20,000 and 40,000 mouse units. The smallest dose to give rise to symptoms has been estimated at around 15,000 mouse units.[198] These figures are decidedly higher than the maximal tolerance for paralytic mussel poison (1200 mouse units per 100 gm. of shellfish meat, or about 2500 mouse units per meal) estimated from feeding tests on primates. This lower figure, adopted by the Food and Drug Administration in regulations on commercial canned shellfish, assures adequate protection against mussel poison. Mussels from regions where they may occasionally become dangerous are sometimes marketed as heat-preserved canned clams.

A recent report of 3 outbreaks of food poisoning following ingestion of asari (*Venerupis semidecussata*) and oyster (*Ostrea gigas*) in Japan lists initial symptoms, after an incubation period of twenty-four to forty-eight hours, as principally gastrointestinal, with leukocytosis, retardation of blood coagulation and disturbance of liver function, followed by death in 34 per cent of the 324 cases observed. A toxic substance designated "venerupin" could be readily extracted from the shellfish, and by any mode of administration it had, in many species of mammals, organotropic, but no neurotropic, effects. It is quite distinct from the mussel poison and is apparently a hitherto unknown shellfish poison.[199]

Fish Poisoning (Ichthyosarcotoxism)

Poisoning due to ingestion of certain kinds of fish has not received the attention it deserves, particularly in the light of experiences during World War II. Halstead,[200-202] Halstead and Bunker,[203] Gudger[204] and Lee and Pang[205] have outlined the economic and military significance of this problem. Aside from a concise knowledge of the taxonomy and biology of fish whose flesh is poisonous, basic research into the chemical and pharmacologic properties of the toxins becomes increasingly important. A review of the relatively vast literature on fish poisoning not readily available to the physician would overshadow the subject under consideration.

The essential facts are, briefly, as follows: ichthyosarcotoxism is classified in three groups — the Pacific type, the Caribbean type (ciguaterra) and the Tetraodon type (fugu, or puffer poisoning). The clinical manifestations, which may develop immediately or within thirty hours of ingestion of the fish meat, are surprisingly consistent. Tingling sensations about the lips and tongue is followed by numbness of the limbs. In 75 per cent of the cases, gastrointestinal symptoms — nausea, vomiting, diarrhea and abdominal pain — are followed by symptoms arising from the central nervous system — joint aches, malaise, chills, fever, profuse sweating, intense itching of the skin, transient painful urination and prostration. Generalized motor inco-ordination, muscular weakness, sensory disturbances, paralysis and irritability are common. The severity of the attacks varies greatly and to some extent depends on the kind of fish involved. Apparently Tetraodon poisoning, affecting many thousands of persons in Japan every year, is the most deadly, the over-all mortality rate being 73 per cent. In the Pacific type the rate rarely exceeds 3 per cent. Victims usually die within five hours of eating the raw or cooked flesh of Tetraodon, widely distributed throughout most warm seas. Not all species of puffers are poisonous. Puffers edible in

one locality (Honolulu) may be poisonous in another (Phoenix Island).[200] Recovery from a severe attack of fish poisoning is usually gradual; weakness may persist for weeks or months. An attack imparts no resistance to subsequent intoxication, and no specific antidote is known.

The Pacific type varies in severity with the type of fish consumed and the place where it is caught. Of the approximately 300 kinds of poisonous fish in the central Pacific, the following are known to have poisonous flesh: humuhumu or trigger fish (*Balistidae* species), opupe or sea bass (*Serranidae, Serranus*), puhi or eel (*Muraenidae, Gymnothorax*),[206] black ulua (*Carangidae, Caraux* species), red snapper (*Lutjanidae, Lutjanus* and *Lethrinus* species), and barracuda (*Sphyraenidae, Sphyraena* species). No reliable statistics on the exact number of species or the incidence of the illness they are capable of producing are available.

Ciguaterra, the type found in the Caribbean region, mostly the Virgin Islands of the West Indies, is severe during the acute phase, but as a rule is not fatal. The ones known to be poisonous are sierra (*Scomberomorus regalis* [Bloch]), cavallas (*Caranx* species), great barracuda (*Sphyraena barracuda* [Walbaum]), groupers (*Mycteroperca* species), amberjack (*Seriola falcata* [Cuv. and Val.]) and other closely related species.

By far the most important is the family of Tetraodontidae — puffers, balloon fish and globe fish, including the well known Japanese fugu. The nature of the poison extracted from the ripe ovaries described as fugu or Tetraodon poison has been carefully studied by Japanese investigators.[207] Even a casual perusal of these and more recent investigations on fish poisoning provides detailed and comprehensive information, but no data concerning the factors, in all probability physiologic or environmental, that cause otherwise edible fish to become toxic. Therefore, it is gratifying to note that the entire field is made the subject of renewed interest by medically trained ichthyologists, who, in co-operation with the pharmacologist, clarify the confused state of knowledge.

The review cannot be closed without a consideration of the so-called Haff disease, an illness that has plagued several countries bordering the North Sea, but may have wider distribution. The following facts and their interpretations are available. About eighteen hours after eating certain fish — perch, bream, roach, eel and burbot — the patient is suddenly seized with acute pain and tenderness in the muscles, except those of the head and face. The merest touch causes agony, and movement is impossible. Urine passed after the onset is brownish black and albuminous, with perhaps a few erythrocytes and leukocytes and granular casts. The reaction for myoglobin is positive. The symptoms pass off in forty-eight hours or so, leaving only slight tenderness and stiffness. There is no rise in temperature. Some patients are repeatedly attacked, whereas others escape altogether. This leads to the idea that there may be some idiosyncrasy. Birds and mammals eating the fish die in considerable numbers. Bacterial and virus infections, plankton or poisoning from factory discharges have been excluded. Some resemblance between Haff disease and the Chastek disease in silver foxes after feeding on raw fish is noteworthy. It is believed that Haff disease may be the result of a disturbance in the metabolism due to the presence in the flesh and liver of certain kinds of fish of an "antivitamin" capable of completely suspending or reducing the biologic action of aneurin.[208]

Conclusion

This review, incomplete in many ways, has attempted to illustrate some of the reasons for the confusion and inadequacy of the present-day knowledge of food poisoning. Probably there is no more fitting conclusion than to repeat the plea that the practitioner and physician, aided by qualified experts in the field of epidemiology and laboratory medicine, jointly subject each outbreak of food poisoning to critical examination. If the analysis has furnished some suggestion about how unwarranted assumptions can be avoided in the future it has fulfilled its hopes.

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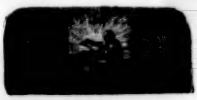
MEDICAL INTELLIGENCE



SUBENDOCARDIAL INFARCTION*

Report of Two Cases

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INDIANAPOLIS, INDIANA

SUBENDOCARDIAL infarction might be defined as irreversible injury caused by prolonged anoxia of the portion of myocardium situated at the farthest point from the blood supply to the coronary artery. Levine and Ford[1] found that the common denominator of the cases reviewed by them was "deficient irrigation, not of a single coronary artery, but of the entire coronary system."

The coronary QS and QR electrocardiographic pattern is believed to be due to the initial transmission of the negative cavity potential toward the exploring electrodes. If the infarction is transmural and no viable muscle is present under the electrode, the cavity potential is transmitted unchanged, and a QS pattern is recorded. On the other hand, if some viable muscle overlies the infarcted area, it contributes to a late positive current, and the QR pattern results. This concept, which stemmed primarily from the work of Wilson and his associates,[2, 3] has been expanded to some extent by the work of Prinzmetal and his group,[4] who showed that the potential within a normal ventricular muscle is negative and that the positivity of the ventricular complex is due to a narrow layer of subepicardial muscle. Consequently, in some patients, infarction involving only the superficial layer of ventricular musculature may result in a QS or QR pattern, in which case the Q wave reflects the negativity of the ventricular wall. Sparing of the subepicardial layer (subendocardial infarction) causes an initial positive deflection (R wave).

It is the presence of the initial R wave that limits the electrocardiographic changes in this form of myocardial infarction to the ST segment (injury) and R wave (ischemia) and deprives the clinician of the diagnostic sign of infarction — namely, the Q wave. As in acute coronary insufficiency, ST-segment depression occurs in all leads that face the uninjured epicardial surface, whereas those that face the cavity show elevation of the ST segment.

The following cases are reported because the electrocardiographic studies were characteristic of the condition under discussion and, coupled with the clinical story, permitted an ante-mortem diagnosis of subendocardial infarction.

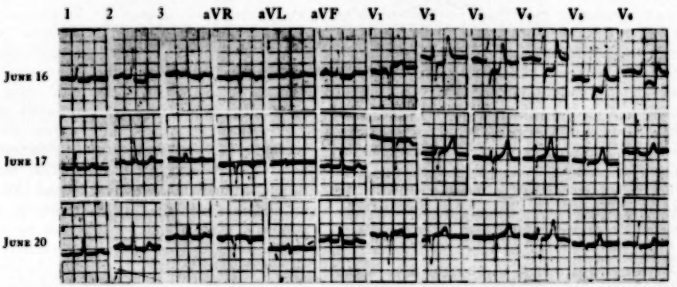

FIGURE 1. *Electrocardiographic Tracings in Case 1.*

CASE REPORTS

CASE 1. A 63-year-old painter was admitted to the hospital on June 16, 1952, complaining of severe substernal pain of 1 hour's duration associated with weakness and profuse perspiration. The chest pain had been somewhat relieved by 15 mg. of morphine sulfate administered before admission.

Physical examination showed the skin and conjunctivas to be pale. The blood pressure was 29/120, and the pulse rate was 84 per minute. The urine was grossly bloody, and the red-cell count was 2,750,000, with a hemoglobin of 7.5 gm. per 100 cc.

The patient improved rapidly with bed rest, oxygen and sedation. On June 23, however, he again began to void grossly bloody urine, with clots of blood. The blood pressure dropped to 130/85. Repeated blood transfusions given slowly failed to improve his

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condition. Bleeding from the bladder continued, and he died 10 days after admission.

An electrocardiogram taken on the day of admission (Fig. 1) demonstrated sagging of the ST segment in all but the aVR and V_1 leads. The T waves in Leads V_2, V_3 and V_4 revealed a marked peaking. The tracings taken on June 17 and June 20 disclosed a return of the ST segment to isoelectric levels, with gradual diminution in height of the T and R waves; these changes were present in all V leads, but were most pronounced in Leads V_2, V_3 and V_4.

At autopsy the heart weighed 425 gm. There was generalized narrowing of the coronary vessels, but no point of occlusion was found. There was a fairly recent infarction of the subendocardial portions of the 2 papillary muscles of the left ventricle. A small scar was noted on the diaphragmatic wall of the left ventricle, indicating an old myocardial infarction. A sessile carcinoma located at the trigone of the bladder was found to be the cause of the hematuria.

Case 2. An 82-year-old man was admitted to the hospital on October 5, 1952, with a 3-day history of vomiting and progressive weakness. He was oriented regarding time, place and person, but was extremely weak. The blood pressure and pulse were not obtainable, and the heart sounds were distant. Laboratory studies showed a red-cell count of 5,130,000, with a hemoglobin of 16.2 gm. per 100 cc.; the carbon dioxide was 20 milliequiv. per liter.

The patient was treated with oxygen, absolute bed rest, morphine and nor-epinephrine. The blood pressure rose to 110/60. The course was rapidly downhill, however, and he died within 24 hours. An electrocardiogram (Fig. 2) revealed depression of the ST segments in all leads except aVR and V_1, where the ST segment was shifted upward, and in aVL and V_2, where the ST segment remained isoelectric.

At autopsy the significant findings were confined to the heart, which weighed 510 gm. Marked narrowing of the coronary vessels was noted, though no actual occlusion was demonstrable. A large area of subendocardial infarction was found involving the anterior wall of the left ventricle and the apex. There was also an infarction of the anterior portion of the septum.

Figure 2. *Electrocardiographic Tracings in Case 2.*

Discussion

The electrocardiographic changes in both cases were characteristic of subendocardial injury. The autopsy examinations seem to support the contention of Levine and Ford that this localized form of infarction is caused by a generalized deficiency of blood to the entire coronary vascular tree instead of to a single vessel.

We believe that the anemia in Case 1 and the prolonged period of vomiting and shock in Case 2, when coupled with impaired coronary flow, resulted in subendocardial infarction. The possibility remains, however, that in Case 2 the shock and vomiting resulted from infarction.

In the differential diagnosis of the electrocardiographic tracings the two patterns that are occasionally confused with subendocardial infarction are the so-called "left-sided heart strain" and "digitalis effect." Careful evaluation of the ST segment and of the history, however, should usually lead to a correct diagnosis.

Summary

Two cases of subendocardial infarction diagnosed ante mortem are presented. The electrocardiographic changes are described, and the absence of the diagnostic feature of infarction — namely, the Q-wave — is stressed.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 39471

PRESENTATION OF CASE

A fifty-nine-year-old married woman was admitted to the hospital because of abdominal pain, nausea and vomiting.

Two weeks before admission the patient noted the gradual onset of nausea and occasional vomiting. Crampy abdominal pain, which was mostly confined to the suprapubic region but was occasionally diffuse, also developed. Two days before admission the abdomen had become quite distended, and she had the severest episode of nausea and crampy abdominal pain, during which she vomited four or five times. During the present illness she had lost 20 to 30 pounds. She had had no chills or fever.

Thirty years before admission she had been told that she needed thyroid, which she had taken ever since (the dose was not stated). She had apparently never been pregnant, and menstruation had ceased at the age of thirty-one. For many years she had taken iron for "low blood count including red blood cells and white blood cells." She had had lupus vulgaris of the right leg that had been treated with radiation and excision. One year previously she had been admitted to another hospital with a chief complaint of migratory discomfort, redness and swelling of the joints of one week's duration. On physical examination there was tenderness on deep palpation in the right lower quadrant, and an abdominal film showed opacities in the right upper quadrant that were thought to be gallstones. The blood pressure on admission was 140 systolic, 80 diastolic. Three hemoglobin determinations ranged from 11.4 to 12.8 gm. per 100 cc., and the white-cell count was 4900, with 54 per cent neutrophils, 45 per cent lymphocytes and 1 per cent eosinophils. A second white-cell count was 8300, with 37 per cent neutrophils, 66 per cent lymphocytes and 2 per cent eosinophils. A blood smear showed normal morphology. The fasting blood sugar was 75 mg., and the nonprotein nitrogen 20 mg. per 100 cc., and the chloride 89.8 milliequiv. per liter. The patient was prepared for a cholecystectomy, but before anesthesia was started, the blood pressure fell to 60 systolic, and the operation was canceled. Subsequently, a basal metabolic rate was −34 per cent, and she was started on thyroid, 0.06 gm. (1 gr.) twice a day. X-ray examination of the skull showed no abnormality. She was discharged with diagnoses of hypothyroidism, cholecystitis with cholelithiasis, and acute appendicitis, recurrent.

Review of the systems revealed that her diet had been inadequate for several years, apparently because of poor appetite. There had been no significant alcoholic intake.

Physical examination disclosed a pale, dehydrated, slightly obese woman with evidence of recent weight loss. Axillary and pubic hair was absent, but there were a few short hairs on the labia majora. The upper extremities and base of the neck showed a brown pigmentation that was thought to be out of proportion to the amount of exposure to sunlight. The pupils were round and equal, but did not react to light or on accommodation. The extraocular movements were normal. Decreased breath sounds and dullness were found at both lung bases; diaphragmatic excursions were poor. The heart was not enlarged, but there were Grade 2 apical and Grade 3 aortic systolic murmurs. The abdomen was distended and presented signs of ascites. There was tenderness in the right upper quadrant and right flank, but no tenderness in the costovertebral angles. A few peristaltic rushes were heard. The liver edge was ballotted 4 fingerbreadths below the right costal margin. On the upper right calf medially there was a brownish discoloration of the skin measuring about 5 by 3 cm.

The temperature was 99.0°F., the pulse 90, and the respirations 24. The blood pressure was 140 systolic, 100 diastolic.

The urine was dark amber and cloudy, had a specific gravity of 1.034 and gave a + test for albumin; the sediment contained 5 red cells and 50 white cells with occasional large clumps per high-power field. Examination of the blood revealed a hemoglobin of 13.2 gm. per 100 cc. and a white-cell count of 7500, with 70 per cent neutrophils, 21 per cent lymphocytes, 2 per cent monocytes, 6 per cent eosinophils and 1 per cent basophils. The nonprotein nitrogen was 17 mg., and the total protein 4.8 gm. per 100 cc., and the chloride 101 milliequiv. per liter. The prothrombin time was 21 seconds (normal, 14 seconds), or 40 per cent, the cephalin flocculation ++ in twenty-four and +++ in forty-eight hours, thymol turbidity 0 units per 100 cc., thymol flocculation negative, and bromsulfalein retention 88 per cent.

Roentgenograms of the chest demonstrated elevation of both leaves of the diaphragm and discoid

areas of atelectasis in both lower lobes. A plain film of the abdomen showed generalized haziness and bulging of the flanks characteristic of ascites. There was a homogeneous increase in density of the pelvis that was thought to be due to free fluid or to a large pelvic mass. The intestinal gas pattern was normal. The bones were osteoporotic, and there was a coarsened texture of the bodies of the second and fourth lumbar vertebras.

On the day of admission a paracentesis yielded 4 liters of cloudy fluid with a specific gravity of 1.010. Pathological examination of the fluid gave no evidence of malignant cells. After the paracentesis no abdominal organs or unusual masses were felt. Seven to ten days after admission the blood sodium was 116 milliequiv., and the chloride 89 milliequiv. per liter, and the total protein 4.9 gm., the albumin 1.6 gm., the globulin 3.3 gm., the total bilirubin 0.9 mg., the alkaline phosphatase 3.7 units, and the cholesterol 101 mg. per 100 cc. The prothrombin activity was 31 per cent, and the bromsulfalein retention 79 per cent. Gastric drainage was guaiac negative. By the tenth hospital day the patient had become drowsy, and had a coarse tremor of the hands. The ascites had reaccumulated. She began to vomit dark-brown and coffee-grounds material; large ecchymoses appeared on the arms, some of which oozed freely. Within a day or two she became comatose. On the thirteenth hospital day, because of a massive hematemesis of bright-red blood, a Seng–Staken esophageal tamponade balloon was inserted. During this day she was anuric; the blood pressure gradually fell from its previous level of 100 to 110 systolic and 60 to 70 diastolic until it became unobtainable. The patient died about an hour later.

Differential Diagnosis

Dr. Philip H. Henneman*: This fifty-nine-year-old woman entered the hospital with ascites and evidence of marked hepatic insufficiency. I am given information suggesting that she had previously had tuberculosis of the skin and now had hypothyroidism, hypoadrenocorticism, possibly hypopituitarism, Paget's disease of the spine and chronic pyelonephritis. It will be difficult to assign all these diverse manifestations to a single disease!

The presence of gallstones and the history of cholecystitis might lead one to suspect that the liver disease was obstructive biliary cirrhosis; however, the virtual absence of obstructive phenomena, such as jaundice, pruritus, hypercholesteremia and an elevated serum alkaline phosphatase, is a strong argument against obstructive cirrhosis. The evidence for failure of the liver's synthetic functions, as evidenced by a low nonprotein nitrogen, hypoalbuminemia, with resultant ascites, and hypoprothrombinemia, is more characteristic of portal cirrhosis. Is information available regarding the cell count of the ascitic fluid? Only the specific gravity and cytologic examination are mentioned.

Dr. Benjamin Castleman: No cell count is recorded.

Dr. Henneman: The removal of 4 liters of ascitic fluid, with its 500 to 600 milliequiv. of sodium, resulted in marked hyponatremia and, probably, in diminution in circulating blood volume. This may have been responsible for the rapid progression of hepatic failure and final death. In retrospect one can say that the course might have been improved if the ascites had been treated by raising the level of the serum albumin with intravenous infusions of human serum albumin rather than by paracentesis.

Some thirty years previously the patient had been told that she was hypothyroid, but she had not continued adequate treatment, as evidenced by the finding of a basal metabolic rate of −34 per cent one year before entry. The descriptive details do not permit me to say that she had myxedema at the time of admission.

She apparently had some degree of adrenal as well as thyroid insufficiency. Evidence for hypoadrenocorticism may include the hypotensive crisis a year previously. During the preparation for anesthesia she probably received a routine dose of morphine, to which patients with hypoadrenocorticism may be extremely sensitive.

Dr. Daniel S. Ellis: The same thing can happen with liver disease.

Dr. Alfred Kranes: Or with myxedema.

Dr. Henneman: That is true.

In addition we note marked hypochloremia on two occasions, loss of axillary and all but a few pubic hairs, brownish pigmentation of the arms and neck, and lack of lymphopenia and eosinopenia during an acute illness.

Pituitary insufficiency is suggested by the precocious cessation of the menses at the age of thirty-one and by the presence of both adrenal and thyroid insufficiency. However, all the endocrine manifestations may have been the consequence of depressed metabolism of the adrenal and pituitary glands during prolonged hypothyroidism. Evidence against this is the observation that in myxedema the ovarian dysfunction is usually menorrhagia and the adrenal insufficiency is usually incomplete and unaccompanied by pigmentation of the skin.

The presence of lupus vulgaris in the past raises the question whether the ascites, the adrenal insufficiency and the pyuria could have been on a tuberculous basis. This is certainly possible; however, the ascitic fluid seemed to have the character of a transudate rather than of a bloody exudate, which is usually found in tuberculous peritonitis. The absence of more impressive hematuria — admittedly, there was only one urinalysis — argues against renal tuberculosis. The urinalysis suggests the common pyelonephritis. Furthermore, tubercu-

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losis would not, as far as I know, explain the hypothyroidism and the marked liver insufficiency.

Two final data are the coarsened texture of the lumbar vertebras, which may have represented Paget's disease of the spine, a very common bony lesion of this age group, and the generalized osteoporosis. The osteoporosis was most probably the consequence of prolonged estrogen lack; however, it has been reported so frequently in association with liver disease, especially biliary cirrhosis, that it is tempting to try to link these two diseases even though no mechanism is known.

I think I need some help from the radiologist at this point.

DR. JOHN F. GIBBONS: The chest films show elevation of both leaves of the diaphragm, particularly the right one, and there is discoid atelectasis in both lower lobes. Two films of the abdomen, one taken in the prone and one in the erect position, demonstrate a generalized haziness over the abdomen, with some loss of the properitoneal fat lines and bulging of the flanks that, together with the high diaphragm, suggest ascites, which we know the patient had. These calcifications in the right upper quadrant are probably gallstones, even though they have a mottled, irregular appearance that is a little different from that of the usual gallstone. The small bowel and colon contain gas, but there is no evidence of intestinal obstruction, and no other soft-tissue masses can be seen in the abdomen. The two lumbar vertebras, the second and fourth, which apparently have an abnormal trabecular pattern, present a very coarse, somewhat striated appearance. There is no evidence of erosion of the pedicles or any other portions of the vertebras and no collapse of any of the vertebras. I think the appearance is quite characteristic of Paget's disease.

DR. HENNEMAN: I cannot prove a relation between all these signs and symptoms, but mention should be made of several possible relations that could have been investigated during life. The endocrine manifestations may have been those of Falta's syndrome or multiple glandular sclerosis[1] — that is, the rare concurrence of fibrosis and destruction of unknown etiology involving the pituitary, adrenal and thyroid glands and often the gonads. In the Ovarian Dysfunction Clinic we have at least 1 patient suspected of having Falta's syndrome. I note that among the 9 autopsies performed on patients with myxedema reported by Means,[2] 2 had absent or fibrotic anterior pituitary glands, and 1 of these had sclerosis of the adrenal cortex as well, perhaps fitting in well with the syndrome of Falta.

Two diseases known to produce severe liver disease and involvement of multiple endocrine glands, though never with complete destruction of all of them as far as I know, are sarcoidosis and amyloidosis. Both these diseases have such protean manifestations that I cannot rule them out; nor can I find sufficient evidence to support them strongly. The past history of lupus vulgaris represents a tuberculous infection that could have been a cause of secondary amyloidosis.

In conclusion, I think she may have had portal cirrhosis of the liver, with terminal necrosis, multiple glandular sclerosis involving the thyroid, adrenal and pituitary glands and probably the ovaries, Paget's disease of two lumbar vertebras and chronic pyelonephritis.

DR. JACOB LERMAN: Would you say that this condition might be explained on the basis of pituitary insufficiency alone?

DR. HENNEMAN: There are a few points against that. She had hyperpigmentation of the arms and legs; patients with untreated panhypopituitarism are remarkable for their lack of pigmentation. Even moles are rare in such patients. Moreover the record states she was slightly obese. It is now recognized that patients with panhypopituitarism do not have the cachexia that used to be attributed to them, but I have never seen one who was truly obese before treatment. On the other hand the patients that Falta described were unusual in that they did have pigmentation of the skin, as in ordinary Addison's disease, and several were moderately obese.

DR. LERMAN: On the other hand only one or two of the glands are involved simultaneously. Falta described patients who had sclerosis of the adrenal and thyroid glands, or sclerosis of the thyroid and some other gland but not all the glands.

DR. CASTLEMAN: Some years ago, in preparing a paper on panhypopituitarism,[3] I read Falta's original paper, in which he reported 2 cases of multiple glandular sclerosis; neither patient had died, and there was therefore no pathological confirmation. He had no evidence for stating there was sclerosis of any of the glands — it was a clinical observation.

DR. LERMAN: Dr. Andries Querido, of Holland, has seen 2 patients at autopsy who had more than one gland sclerosed — the thyroid and the adrenal glands.

DR. CASTLEMAN: We have seen atrophy of endocrine glands a number of times with panhypopituitarism, but I do not think we are justified in using the term "Falta's syndrome."

DR. HENNEMAN: In ordinary panhypopituitarism one would expect decrease or atrophy of adrenal tissue, but some tissue should remain. My understanding of Falta's syndrome is that there is almost total destruction of the glandular tissue, leaving only a fibrous scar.

DR. CASTLEMAN: I do not believe Falta ever had pathological evidence.

DR. ELLIS: I should like to ask Dr. Henneman what additional therapy he would have given this patient since he raised the problem of pituitary insufficiency. Clinically, we were confronted with a rapidly deteriorating patient with several emer-

gencies so we did not pay much attention to the fact that she might have had pituitary insufficiency.

DR. HENNEMAN: It appears that serum albumin might have been a more desirable way of treating the ascites since we believe hypoalbuminemia to be the most important factor in the genesis of ascites. Our current therapy for pituitary insufficiency relies most heavily on cortisone, which makes the greatest difference in the general health of the patient and which is essential for survival in acute illness. Desiccated thyroid and testosterone are also of value in this disease.

DR. ELLIS: The patient did receive some cortisone but only in the last forty-eight hours; she was also given serum albumin, which precipitated the bleeding. She was admitted to the Surgical Service for the diagnosis of ovarian tumor, and the paracentesis was done as a diagnostic measure to determine whether this was a local abdominal swelling or whether it was ascitic fluid. It is certainly true that the sodium depletion may have resulted from the abdominal paracentesis; on the other hand such patients usually get into trouble much more rapidly after the paracentesis than this patient did. It was fully a week after the paracentesis that she began to deteriorate rapidly.

DR. JOHN B. STANBURY: I should be less impressed that the evidence supported abnormalities of several glands than that it suggested thyroid disease along with the liver disease, which she clearly had.

DR. LERMAN: What about the hypogonadism? She had not menstruated since the age of thirty-one.

DR. STANBURY: That is possible.

CLINICAL DIAGNOSES

Cirrhosis of liver.
Esophageal varices.

DR. PHILIP H. HENNEMAN'S DIAGNOSES

Portal cirrhosis of liver, with terminal necrosis.
Multiple glandular sclerosis, thyroid, adrenal and pituitary glands and ?ovaries.
Paget's disease of spine.
Chronic pyelonephritis.

ANATOMICAL DIAGNOSES

Fibrosis of anterior lobe of pituitary gland, with secondary atrophy of thyroid and adrenal glands and ovaries (panhypopituitarism).
Hemochromatosis, severe, generalized.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: This was a fascinating case for the pathologist. The liver was very shrunken, weighed only 760 gm. and had a peculiar chocolate color. A microscopical section stained for iron demonstrated a great deal of hemosiderin and extensive fibrosis — a clear-cut case of hemochromatosis. The pancreas was atrophic and contained fat and a great amount of hemosiderin deposited not only in the acinar cells but also in the islets and ductile epithelium. Hemosiderin was present in every organ of the body, including the heart, in which individual fibers were loaded with it.

Very little of the pituitary gland could be found. At the base of the sella turcica, which was a large hole, we found some scraps of connective tissue from which Dr. Agnes S. Burt made serial sections. This tissue weighed 100 mg., in contrast to the normal weight of the pituitary of about 600 gm., and was for the most part posterior lobe. In the small bit of anterior lobe that was present, the cells were markedly separated by loose hyalinized connective tissue. There certainly was little evidence of function in the anterior lobe.

The thyroid gland was also reduced to less than a gram of tissue. Here, again, serial sections were prepared; these showed diffuse scarring with severe lymphocytic infiltration and hemosiderosis; the acini contained colloid. The parathyroid glands were full of iron but otherwise normal. The adrenal glands were about a third the normal size, and the ovaries were also quite small. This schematic drawing shows the relative sizes of the endocrine glands in this patient and in a normal postmenopausal woman (Fig. 1).

DR. HENNEMAN: Did the ovaries contain hemosiderin?

DR. CASTLEMAN: Not very much.

We do not usually see hemochromatosis in females, but the fact that this patient had not had any menses since the age of thirty-one probably put her in the same class as a male and thus made her eligible for hemochromatosis. If one saw the thyroid gland alone, one might try to infer that scarring due to hemosiderin deposits had produced the marked atrophy; however, I think the atrophy had occurred secondary to the pituitary changes before the onset of hemochromatosis. Also, the patient had signs of hypothyroidism at the age of thirty when she almost certainly did not have hemochromatosis. I believe we have to indict the endocrine glands as being diseased long before the hemochromatosis developed — all the findings fit in with panhypopituitarism. Surprisingly enough, there was no evidence of diabetes. It will be recalled that this patient's blood sugar was only 75 mg. per 100 cc. I do not remember having seen another case with so much hemochromatosis in the pancreas without diabetes. It is quite possible that she was protected by the atrophy of the adrenal glands and of the pituitary gland.

Should you like to comment about this point, Dr. McArthur?

DR. JANET W. MCARTHUR: I might say a word about the failure of diabetes to develop. From the classic investigations of Houssay and Biasotti[1]

we know that hypophysectomy produces a striking amelioration of diabetes in depancreatized animals. This amelioration is thought to be due to the withdrawal from the circulation of the so-called diabetogenic hormones of the pituitary — growth hormone, adrenocorticotrophic hormone, thyrotropic hormone and, at least in some species, prolactin. From the studies of Long and Lukens[5] we also know that removal of the target endocrine glands upon which these pituitary hormones act will ameliorate diabetes. If the thyroid gland is

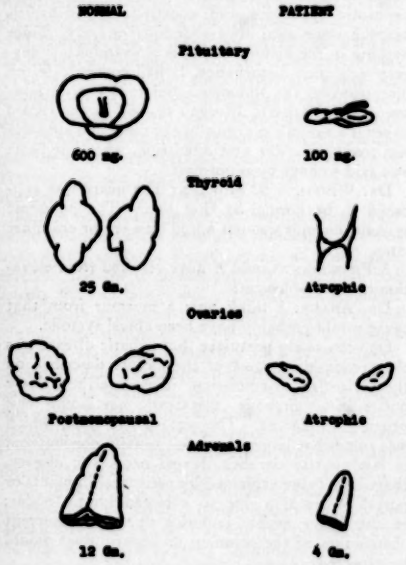

FIGURE 1. *Endocrine Glands of the Normal Postmenopausal Woman Compared with Those of the Patient.*

removed, there is a slight reduction in the severity of pre-existing diabetes; if the adrenal cortex is removed, there is a much greater reduction.

In this particular case there was still another factor that tended to suppress any diabetic tendency: the presence of liver disease. It is well known that certain diabetic patients who develop cirrhosis of the liver experience a lessening of the severity of their diabetes. However, this phenomenon is by no means a universal occurrence, and in this patient it seems reasonable to infer, as Dr. Castleman has done, that diabetes was prevented from manifesting its presence as a result of the remarkable experiment of nature, which effected a "prophylactic hypophysectomy."

DR. CASTLEMAN: The immediate cause of death was hemorrhage from esophageal varices.

DR. ELLIS: What part do you think her taking of iron for thirty years played in the pathogenesis of the hemochromatosis?

DR. CASTLEMAN: We were unable to find out how much iron she had taken to determine whether the hemochromatosis was exogenous. It may have been an aggravating factor, but I do not know that we can be sure of it. Our last case of hemochromatosis in a woman was considered to be exogenous, the result of the taking of large amounts of iron by mouth.[6]

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CASE 39472*

PRESENTATION OF CASE

First admission. A sixty-five-year-old man was admitted to the hospital because of diarrhea.

He had been in good health until four weeks previously, when he noted abdominal fullness with an increase of stools to four times daily, accompanied by blood streaking. There had been no nausea, vomiting or hematemesis. He had not lost any weight. There was no history of jaundice or alcoholism.

Examination of the heart and lungs was negative. The abdomen was distended, with shifting dullness. Peristalsis was normal. The liver edge was firm and was felt 8 cm. below the right costal margin. The spleen was not felt. There was no jaundice, spider angiomas or gynecomastia. Rectal examination showed large external hemorrhoids.

The temperature was 98°F., the pulse 80, and the respirations 20. The blood pressure was 120 systolic, 78 diastolic.

Urinalysis was negative. The hemoglobin was 15.5 gm. per 100 cc., and the white-cell count 5400, with 79 per cent neutrophils. The red cells were normal on smear. The total serum protein was 6.6 gm., with an albumin-globulin ratio of 1, the nonprotein nitrogen 31 mg., the alkaline phosphatase 13 units, and the total serum bilirubin 1 or 2 mg. per 100 cc. The prothrombin time was 18 seconds (normal, 14 seconds); the bromsulfalein test revealed 38 per cent retention of the dye in 45 minutes, and the cephalin flocculation was +++ in forty-eight hours. Several stool guaiac tests were negative. Two

*Presented at a course for graduate students in internal medicine.

abdominal paracenteses obtained 7600 cc. of clear, amber fluid with a specific gravity of 1.011. The fluid had a total protein of 860 mg. per 100 cc. and 448 red and 117 white cells per cubic millimeter, with 47 per cent neutrophils and 70 per cent lymphocytes. A cell block and cytologic smear of the abdominal fluid were negative for tumor cells. X-ray films demonstrated minimal varices of the distal esophagus, a small hiatus hernia, an old deformity of the duodenal bulb and an enlarged liver and spleen. Abdominal films showed massive ascites. No gross lesion was demonstrable by a barium-enema examination. Sigmoidoscopy disclosed an edematous mucosa and hemorrhoids.

The patient was placed on a 3000-calorie, high-protein, low-salt diet and discharged on the twenty-fourth hospital day.

Final admission (eighteen days later). The patient had been feeling fairly well until the day before admission, when he had a chill and a temperature rise to 103°F. He became worse on the day of admission; pulmonary rales were noted by his physician. He was given 0.4 mg. of Cedilanid intravenously and later 0.2 mg. of digitoxin by mouth as well as a subcutaneous injection of 1 cc. of Thiomerin. He was also given penicillin and 10 mg. (1/6 gr.) of morphine, as well as 20 mg. (1/3 gr.) of Pantopon.

The temperature was 99°F., the pulse 88, and the respirations 28. The blood pressure was 90 systolic, 70 diastolic.

Physical examination showed marked jaundice. The patient was drowsy, and breathing was shallow. The pupils were small but not pin-point and did not react to light. The diaphragm was high, and there were bilateral fine pulmonary rales. The cardiac apex was percussed 11 cm. to the left of the midsternal line. The rhythm was regular, and the sounds were of good quality. There was a Grade 2 pulmonic systolic murmur. The abdomen was protuberant, with flank dullness, and there were distended veins in the upper midportion. A hard, nontender liver was palpated in the epigastrium. Splenic dullness was percussed, but the edge of the spleen was not felt.

Urinalysis showed ++ tests for albumin and bile; the sediment contained many hyaline casts. Examination of the blood disclosed a hemoglobin of 16.8 gm. per 100 cc. and a white-cell count of 15,300, with 88 per cent neutrophils. Other chemical determinations and an examination of the abdominal fluid gave about the same findings as before. A throat culture grew out abundant growth of *Haemophilus influenzae*, *Staphylococcus aureus* and diphtheroids, moderate growth of *Neisseria catarrhalis* and nonhemolytic streptococcus and a few beta-hemolytic streptococci. Blood cultures grew out Group C salmonella in four flasks.

On the first hospital day the temperature rose to 101°F.; thereafter it ranged between 98.4 and 100°F. The course was downhill with fetor hepaticus, deepening jaundice and finally coma. On the fourth hospital day blood was noted oozing from the rectum. The patient went into shock, the blood pressure being unobtainable in spite of three transfusions, and died. It was estimated that he had lost about 1 liter of blood by rectum.

Differential Diagnosis

Dr. F. Dennette Adams*: Ascites and enlargement of the liver in the absence of any of the usual causes of anasarca such as congestive heart failure, nephrotic syndrome and constrictive pericarditis bespeak some local intra-abdominal malady. Since nothing in the history or physical examination suggests any such disturbance, I shall concentrate my discussion on the abdomen. Before doing so, however, may I ask Dr. Morgan to look in the record to see if a systolic murmur in the pulmonic area was reported during the first admission, when the heart was said to have been normal?

Dr. Winfield S. Morgan: The heart was supposed to be normal at that time. The pulmonic systolic murmur was not noted by a senior examiner later.

A Physician: Could it have resulted from elevation of the diaphragm?

Dr. Adams: I think not; a murmur from that cause would probably have been apical systolic.

One can safely postulate that hepatic disease was the predominant cause of the picture described on the patient's first admission. There are three likely possibilities: cirrhosis, metastatic carcinoma and primary carcinoma. The size of the liver, which was somewhat larger than that usually encountered in later portal cirrhosis, favors neoplastic disease, the ascites being explained by peritoneal implants or portal obstruction due to enlarged lymph nodes; in the latter event, jaundice due to concurrent obstruction of the common or hepatic duct would be expected.

A Physician: Why was gynecomastia specifically mentioned?

Dr. Adams: The cirrhotic liver cannot conjugate estrogenic hormone so that gynecomastia is likely to develop in a man and abnormal uterine bleeding in a woman — even long after the menopause. We regard both gynecomastia and spider angiomas, when found, as important indications of parenchymal liver disease.

Except for the size of the liver and the possibility that the ascites was due to peritoneal implants, there is nothing in the record of the first admission to support a diagnosis of carcinoma. On the other hand, there is plenty to accent primary intrahepatic disease: the large liver, the ascites, the various laboratory studies, especially the albumin-globulin ratio, alkaline phosphatase, cephalin-flocculation

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response, bromsulfalein test and x-ray detection of esophageal varices and enlargement of the spleen. Large hemorrhoids might be regarded as an indication of a blood shunt from the portal to the inferior vena cava system, but so many otherwise normal persons have hemorrhoids that they cannot be emphasized in this connection. It might well be asked if these abnormal laboratory findings could have been due to malignant infiltration of the liver rather than cirrhosis. In my opinion they could not: in metastatic or primary carcinoma, except in the presence of biliary-tract obstruction or occasionally in the terminal stage, enough normal liver parenchyma remains to handle the metabolic load so that functional impairment is not striking.

The hemoglobin at the upper level of normal and the normal appearance of the red cells are unusual in advanced cirrhosis; they give one pause for thought. But it is a good working rule not to be too strongly influenced by one or two laboratory tests that do not conform to the expected pattern. In this case the other tests were so definitely indicative of liver impairment that the hemoglobin and red-cell findings must be disregarded.

Failure to find malignant cells in the ascitic fluid by no means excludes neoplastic disease. Yet there is no other evidence for it except, as noted previously, that the liver was perhaps larger than one usually finds in late portal cirrhosis. My diagnosis for the first admission is cirrhosis of the liver. If one must be disturbed by the liver size, one could speculate about the possibility of a superimposed hepatoma, but this could only be speculation since there was no definite indication. Absence of excessive alcohol intake or anything suggesting liver disease in the past is not inconsistent with the diagnosis of cirrhosis. Dr. MacMillan, will you please describe the x-ray findings?

DR. ALEXANDER S. MACMILLAN, JR.: The first examination, a barium-enema examination, is not satisfactory; the patient was not well prepared, and the film technically is poor. In films of the gastrointestinal examination there is evidence of esophageal varices. No obvious gastric lesion is noted. The duodenal bulb shows a clover-leaf deformity without a definite crater. There is evidence of increased fluid within the peritoneal cavity. The spleen may be enlarged, and the hepatic flexure is lower than usual, suggesting liver enlargement.

DR. ADAMS: Was there a hiatus hernia?

DR. MACMILLAN: Yes; but it is small. It is not uncommon at this age and is usually without clinical significance.

DR. ADAMS: It is significant only as a third possible cause for bleeding; in this case varices would rate first, and the old ulcer second. Even though the radiologist may think an ulcer is healed and is not able to demonstrate a crater, the lesion may be active and a source of bleeding.

The evidence gathered during the second admission confirms that found previously and seems to support the diagnosis of cirrhosis. Certainly, nothing is presented to justify changing one's opinion regarding the basic illness. Physical examination and liver-function studies were virtually the same. I am not impressed by the statement that splenic dullness was percussed: percussion in this area in the presence of both a large liver and ascites is by no means dependable. However, we do have the x-ray films to fall back on.

The pulmonary rales, judging from the treatment given, appear to have alerted the patient's family physician to the possibility of cardiac failure, but there is no specific indication of this complication. The rales could have been due to a bronchopulmonary process appearing in a poor risk, with obvious superimposed infection as indicated by the chill, fever and elevated leukocyte count, or merely to basal atelectasis secondary to the elevated diaphragm.

The jaundice, drowsiness and, later, coma can be entirely attributed to liver failure, which, in turn, could well have been hastened by the infectious process. The morphine and Pantopon also may have contributed to the decline; these drugs are likely to cause trouble in a person with serious liver impairment and must be given with great caution.

One can only speculate about the start of the infection that, I believe, hastened the patient's death. Remembering that he had diarrhea at the time of the first admission, one can readily assume that this was the beginning of the trouble; it smouldered along for the intervening weeks, eventually developing into overwhelming blood-stream infection. We know that systemic colon-bacillus infection is likely to develop in a patient with severe liver impairment; perhaps in this case, the liver disease enabled the salmonella organisms, which might otherwise have been relatively innocuous, to gain a strong foothold.

One more question, Dr. Morgan. Does the record show that the patient received penicillin during the first admission?

DR. MORGAN: No; he did not.

DR. ADAMS: I asked that question because we know that penicillin may open the gate for penicillin-resistant organisms. If penicillin therapy had been administered, one could well wonder if it contributed to the severity of the salmonella infection. But this is all speculation. The infection may have started independently just before the second admission.

One must mention the possibility of terminal acute bacterial endocarditis. It should be remembered that during the second admission a systolic murmur in the pulmonic area was reported; it presumably had not been present previously. Acute bacterial endocarditis, in contrast to the subacute form, can appear on a normal valve. Therefore, one cannot escape the thought that the appearance of the pul-

monic murmur (if actually it did appear) was the result of a vegetation on the valve due to infection that started at the time of the first admission. This possibility is supported by the recovery of salmonella in four blood-culture flasks.

Was hemorrhage a factor in the death? Again, one can only speculate. Liver failure or infection, or both, could have been entirely responsible for the terminal state of shock. Hemorrhage from the esophageal varices may or may not have been present. The stomach may well have been full of blood at the time of death.

My diagnoses are cirrhosis of liver, with liver failure, terminal septicemia, ? acute bacterial endocarditis and ? bleeding from esophageal varices.

DR. VICTOR G. BALBONI: Did you assume that the infection tipped him into liver failure?

DR. ADAMS: Yes.

A PHYSICIAN: Do you mean the salmonella infection?

DR. ADAMS: Yes. That seems well established by the blood cultures. Cholangitis from ascending infection is not at all likely; the liver would have been tender, and the white-cell count higher.

CLINICAL DIAGNOSES

Cirrhosis of liver.
? Hepatoma.

DR. F. DENNETTE ADAMS' DIAGNOSES

Cirrhosis of liver.
Terminal septicemia.
? Acute bacterial endocarditis.
? Bleeding from esophageal varices.

ANATOMICAL DIAGNOSES

Hemochromatosis of liver.
Hepatoma, diffuse.
Esophageal and hemorrhoidal varices.
Splenomegaly.

PATHOLOGICAL DISCUSSION

DR. MORGAN: The diagnosis of cirrhosis was correct, Dr. Adams, but there was a little more.

DR. ADAMS: I should have added "question of hepatoma"; that is a common complication of cirrhosis.

DR. MORGAN: At autopsy the pericardial cavity contained about 450 cc. of serosanguineous fluid, and the heart was of normal size and completely normal. There was no evidence of a bacterial endocarditis. I do not know how to explain the pulmonic murmur.

DR. ADAMS: Perhaps it was there at the first admission and not regarded as important. A pulmonic systolic murmur in childhood or early adult life is often unimportant, and is more likely to be significant in later life.

A PHYSICIAN: Could it have been functional?

DR. ADAMS: Yes, but rare at this patient's age. Incidentally, I think "physiologic" is a better term for the unimportant murmur.

DR. MORGAN: The lungs were congested and edematous, weighing about 1000 gm. There was a congestive splenomegaly (weight of 600 gm.). The liver weighed 3100 gm., somewhat more than twice the normal weight, and showed severe nodularity throughout. Two types of nodules were present, one in which the nodules were reddish-brown measuring 2 to 6 mm., apparently representing remaining cirrhotic liver tissue and the other being composed of yellowish, often necrotic, tumor tissue forming masses up to 10 cm. in size. These tumor nodules were scattered diffusely throughout both lobes. Tumor had also metastasized to lymph nodes of the porta hepatis and had extended into the portal vein, occluding it almost completely for a distance of 2 cm.

Microscopically, the cirrhotic process proved to be one of hemochromatosis. Hemosiderin pigment was also present in considerable amounts in the acinar cells as well as the islands of Langerhans, and it is of interest that despite the involvement of the islet cells this patient did not have any evidence of diabetes.

Regarding the rectal bleeding terminally, esophageal varices were present as shown on the x-ray films, but these were not ulcerated, and there was no blood in the stomach or intestines. There were, however, large hemorrhoidal varices, which we believe accounted for the severe loss of blood. In our experience such varices are a rare source of massive hemorrhage, but in this case they seem to be a valid explanation since there was no blood higher up in the gastrointestinal tract and no other source was found.

Concerning the salmonella septicemia, we could find no evidence of infection in the intestines. Along this same line, however, Dr. Adams will recall a case that we had very recently* of a woman who also had a salmonella infection with a mycotic aneurysm that ruptured; in that case there was, again, no sign of enteritis.

*Case Records of the Massachusetts General Hospital (Case 39291). *New Eng. J. Med.* 249:110-115, 1953.

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TOXOPLASMOSIS

AN article in the *Journal* six years ago[1] called attention to the increasing medical importance of toxoplasmosis, a parasitic disease that was being recognized in widely separated areas. The recent publication of six papers[2-7] given in a symposium on the subject organized by the American Society of Tropical Medicine and Hygiene and the recent notification[8] by the Massachusetts Department of Public Health of a laboratory service that is now available for the serologic diagnosis of toxoplasmosis re-emphasize the gravity of this disease.

Studies of toxoplasmosis in recent years have centered on laboratory investigations furthering knowledge of the biology of the parasite, the pathology of the infection, the mode of transmission, the development and use of additional serologic tests for diagnosis and study of the epidemiology of the disease and the search for effective chemotherapeutic methods of treatment.

The parasite, *Toxoplasma gondii*, is not new, having been discovered in 1909. The diverse types of acquired and congenital disease that can be produced by this organism,[6,7] the existence of latent infections as determined by serologic tests without manifest disease, and the widespread spontaneous infections of wild and laboratory animals make toxoplasmosis a difficult condition to diagnose and control. Apparently, there is no immunologic difference between strains originating from diverse areas of the world and those from different species of animals, but virulence varies. That this parasite can cause acute infection with irreversible tissue damage that terminates fatally has now been shown with sufficient frequency to warrant exhaustive diagnostic efforts if the infection is suspected. The enigma, however, of widespread asymptomatic infection with the production of acute disease in the fetus, in children occasionally and in adults only rarely indicates either that in most cases the infecting dosage is too low to produce disease or that the host is able to control the virulence of the parasites by natural resistance or immunity.

Thus far the mode of transmission of the organism from host to host is still unknown. It is known that the transmission can take place *in utero* from an infected mother to the embryo, but observation from naturally acquired and experimentally induced infections with a variety of arthropod vectors has failed to reveal usual routes of infection or to incriminate specific blood-sucking arthropods as vectors. Physicians caring for patients with suspected toxoplasmosis, however, should make every effort to inquire about bites by arthropods or exposure to animals.

The most striking advances in knowledge of infection in human beings have come from the application of a new serologic test, the cytoplasm-modifying or dye test of Sabin et al.[9] When this procedure is used along with the complement-fixation test, physicians are better able to determine the presence of the infection, the course of the disease and its distribution in the general population. These two serologic tests, however, need to

be supplemented by attempts to isolate the parasites in toxoplasma-free susceptible animals, such as hamsters, white mice and guinea pigs, blood, exudates or biopsy specimens from patients being used. Studies of serums from eight normal population groups by Feldman[6] (1953) from the Arctic to tropical areas have shown that antibodies for toxoplasma exist in 10 to about 70 per cent of the population in Iceland and Tahiti, the incidence in the United States ranging between approximately 17 and 33 per cent.

The occurrence of a fatal case of acute toxoplasmosis in Boston in 1950[10] and the patient's failure to respond to the great variety of agents, such as sulfonamides, antibiotics and antimalarial drugs, demonstrate the difficulties in treatment. It now appears from the work of Summers,[11] Eyles[7] and others that sulfonamides and the pyrimidine drug, Daraprim, possess therapeutic effects against experimental toxoplasmosis in animals, a lead that may show the way to the discovery of an effective agent to treat the disease in human beings. These drugs have specific effects and when given together act synergistically with each other. Studies to date have been confined to acute infections in animals, and it is not known whether or not similar beneficial results can be obtained with chronic infections.

The rapid increase in knowledge of toxoplasmosis is a tribute to the American scientists and clinicians[12] primarily responsible. Clinicians should be on the lookout for syndromes that suggest toxoplasmosis and seek help through experts and through the Serologic Diagnostic Service of the United States Public Health Service to verify the diagnosis. This co-operation will enable them to assess the public-health importance of human toxoplasmosis and encourage the continuation of research already under way to solve still unanswered problems of transmission, control and therapy.

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CORTISONE AS AN ADJUNCT IN TREATMENT OF TUBERCULOUS MENINGITIS

One of the most difficult and yet most momentous tasks for the physician is the evaluation of new methods of treatment. Widespread and uncritical acceptance of relatively untested methods of therapy may, at times, lead to needless hazard, expense or discomfort to the patient. The physician's responsibility for withholding potentially dangerous treatment unless there is clear evidence of its value is surely as great as the more commonly stressed responsibility of becoming familiar with new methods as they appear.

Cortisone and its congeners have been demonstrated, in many ways, to depress resistance to infection and to affect adversely the course of many infections, including tuberculosis.[1] However, because these hormones alter fibrogenesis and inhibit connective-tissue responses to many injurious stimuli, it is reasonable to investigate whether the formation of excessive amounts of connective tissue, in situations in which such formations are undesirable, might not be inhibited by judicious use of steroid hormones. Even under carefully controlled conditions, the connective-tissue response to various stimuli appears to be inhibited in a variable and unpredictable manner, and the effect of ordinary doses of adrenocortical hormones on fibrogenesis is not always demonstrable clinically, although such effects are quite reproducible with large doses of hormone in laboratory animals.[2] Furthermore, there is general agreement that preformed connective tissue is very slightly, if at all, affected even in the experimental situation in which large doses of hormone may be given over long periods.[3]

Nevertheless, the possibility of inhibition of connective-tissue reactions by adrenocortical hormones

is sufficiently attractive to warrant further study in diseases such as tuberculous meningitis in which late scarring may account for some of the most difficult complications that arise. Thus, cortisone might be given early in the disease to prevent the formation of adhesions, or it might be given after adhesions have formed, in the hope of inducing lysis or of hindering the formation of more adhesions. There are few data that bear on these possibilities. It appears well established not only that resistance to tuberculosis is depressed by the adrenal steroids but also that the combination of streptomycin and cortisone is less effective than streptomycin alone in the treatment of experimental tuberculosis.[4] The premise that sufficient antimicrobial therapy will suppress the spread of tuberculous infection that might occur as a consequence of the administration of adrenal steroids therefore seems to require further and most cautious study. This premise implies, in effect, that the host factor can be de-emphasized if sufficient antimicrobial therapy is used; it is doubtful if many phthisiologists would accept the validity of such a concept.

Whether cortisone will prove of benefit in established cases of tuberculous meningitis, in which subarachnoid block has developed, remains to be decided. Elsewhere in this issue of the *Journal* is a report of 7 cases of tuberculous meningitis, some with subarachnoid block, treated with cortisone and antimicrobial drugs. The authors view their results with justifiable optimism, but are wisely circumspect in claiming no more than that these preliminary observations indicate the need for further study. A small number of patients were treated in a similar manner by Kinsell,[5] who believed that his results also were encouraging. On the other hand, Barnard[6] found no advantage in the use of cortisone in the treatment of 30 patients with tuberculous meningitis by intrathecal and oral administration of cortisone along with the usual antibiotics. Although the data are not reported in detail, and hence cannot be analyzed adequately, the author states that there was no significant effect on neurologic or mental changes, that no evidence of accelerated resolution of the basal exudate was obtained clinically or at autopsy, and that attempts to decrease the numbers of deaths occurring during the first ten days gave disappointing results. It is not possible to tell, from this brief report, whether cortisone significantly affected the over-all recovery rate.

For proper evaluation the data must be compared with recent evidence concerning the prognosis in tuberculous meningitis.[7] Current methods of treatment have reduced the over-all mortality in an adult group to about 35 per cent, and there is every reason to believe that the more widespread and vigorous use of isoniazid along with streptomycin and para-aminosalicylic acid will lower this figure still further.

An interesting possibility that has appeared recently is that hydrocortisone, which, unlike cortisone, inhibits fibrogenesis when applied locally, may be given intrathecally and inhibit the connective-tissue response to the intrathecal administration of irritants. Preliminary data suggest that the generalized systemic effects of adrenal steroids may be avoided, in part at least, by the administration of hydrocortisone in this manner.[8] However, preliminary observations on the intrathecal use of hydrocortisone in tuberculous meningitis suggest that it offers no advantage over cortisone.[6]

Not many years ago, when the outcome of tuberculous meningitis was uniformly fatal, it was not difficult to recognize an effective treatment. However, as various methods of treatment have emerged, all of which are to some degree effective, only carefully controlled observations can be expected to elicit all but the most marked differences in effectiveness of these various procedures. Until such studies are completed, the use of cortisone and related compounds in tuberculous meningitis is a highly experimental procedure that appears safe enough to warrant further clinical trial, but only under controlled conditions permitting a reliable evaluation of potential advantages and disadvantages in comparison with accepted procedures.

References

1. Editorial. Deleterious effect of ACTH and cortisone on tuberculosis. *New Eng. J. Med.* 245:662-664, 1951.
2. Ragan, C., Howes, E. L., Plotz, C. M., Meyer, K., and Blunt, J. W. Effect of cortisone on production of granulation tissue in rabbit. *Proc. Soc. Exper. Biol. & Med.* 72:718-721, 1949.
3. Curran, R. C. Effect of cortisone on reaction of mouse peritoneum to quartz. *Brit. J. Exper. Path.* 33:82-86, 1952.

4. Spain, D. M., and Molomut, N. Effects of cortisone on development of tuberculous lesions in guinea pigs and on their modification by streptomycin therapy. *Am. Rev. Tuberc.* 62:337-344, 1950.

5. Kinsell, L. W. Infectious diseases. In *Proceedings of the Conference on the Effects of Cortisone, Dec. 29, 1951.* 62 pp. Rahway, N. J.: Merck & Company, 1951. Pp. 49-53.

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7. *Transactions of the 12th Conference on the Chemotherapy of Tuberculosis. Held on February 9 to 12, 1953, at the Fulton County Medical Society, Atlanta, Georgia.* 430 pp. Washington, D. C.: Veterans Administration, Central Office, 1953.

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THANKSGIVING

THANKSGIVING, particularly in New England, which has adopted it for a sort of special regional observance, can have its significance tailored to the mood of him who contemplates it. A day of football, of feasting and of fallen leaves, it conjures up automatically a mental picture of the very end of the harvest season. The thought of it is a perennial reminder of Pumpkin Hollow — of cider presses and glass jugs and piles of apples and of squashes, and of an urgency about getting the rest of the crop under cover.

Coming two moons after the long harvest moon and a month beyond the hunter's it is a sign that the sedate autumnal bacchanal (limited to sweet cider) is coming to an end, that the fleeting season of golden light and changing colors has gone with the November rains; that the little shallow ponds have had their first skimming of ice, and winter is around the corner.

It is this storing of the harvest, as much as the earlier, more spectacular gathering of it, that gives Thanksgiving its greatest material as well as its spiritual significance, for it represents thrift and foresight in planning for the long months when earth takes its own winter holiday. With nature's productive period over it is time to give thanks where thanks belong for those blessings that have come in greater or less measure, and to be grateful for the added strength that even adversity has brought. For the hard road may be the wholesome one, and the stubborn soil, by its resistance, contributes to the character of him who plows it.

Despite the confusions and misunderstandings that still exist among the races of men, there is much this year for which to be thankful. We in America may be thankful that we have great problems to face and obstacles still to be overcome. We may be thankful for that lack of security that keeps us alert, as well as for a return to peace, however uneasy. Half-blinded by international jealousies and misunderstandings and deafened by the ululations of those who love to ululate, we may be thankful that there has been brought into being an assembly of nations before which international difficulties may be discussed. We may be thankful for the advances in medicine that the year has brought and for the progress that has been made, however slowly, in the extension of gracious medical service.

We may be thankful that we have not yet been rocked in the cradle of that paternalistic welfare that releases us only at the grave.

LASDON GRANTS

WILLIAM S. LASDON, president of the Lasdon Foundation, Inc., of Yonkers, New York, recently announced the awarding of 26 grants to universities and medical centers throughout the United States and abroad. The total sum to be expended in this way for "the primary goal of humanitarian service through scientific research" amounts to $178,092.54.

Among the special grants is one of $15,000 to Harvard Medical School for further investigations into the transplantation of the human kidney, and one of $15,856 to Washington University of St. Louis, Missouri, for research in hypertension and other vascular diseases.

By such unrestricted grants from public-spirited philanthropists and foundations, even if for designated purposes, scientific investigation will be able to retain a freedom that might be lost if its support was confined to any single source.

Dr. Greenby was recently tried for seduction, in Kentucky, which the indictment alleged was accomplished by first administering internally Spanish flies to Miss Malvina Kelly. . . . A more absurd notion never had vulgar currency, than that blistering flies excite immoderately the animal passions.

Boston M. & S. J., *November 23, 1853*

MASSACHUSETTS MEDICAL SOCIETY

LOUIS EUSEBE PHANEUF

1884–1953

Louis E. Phaneuf was born on February 27, 1884, at St. Hilaire, Quebec. His father, Henri, was a contractor, and his mother, Laurette (L'Heureux), before marriage a schoolteacher. Louis was the oldest of seven children, the Reverend Phillippe Phaneuf, pastor of the church of St. Mathias sur Richelieu, being the youngest. At his funeral service in St. Ignatius Church, Chestnut Hill, his brother, the Priest, chanted the prayers of the High Mass for the Dead, in which many participated: those who had worked with him at hospital and school; the Sisters of Charity of the Order, St. Vincent de Paul, and nurses trained by them; residents and interns, many members of the staff of the Carney Hospital and representatives of other hospitals; the Chaplain of the Carney Hospital; students and teachers; members of the American Board of Obstetrics and Gynecology, on which he had been a director; former patients and friends; and a sister, four brothers and his wife.

His early years were little different from those of others of his day and habitat. His penmanship and attention to detail were noteworthy in grade school. The requirement at the Massachusetts College of Pharmacy that one reach the age of twenty-one years before receiving a degree resulted in a year of postgraduate work. This completed, he was given two degrees in pharmacology in 1905. Occasionally, he spoke of his worthwhile experiences when he managed the drugstore of his late uncle, Pierre Octave L'Heureux, in Ware, Massachusetts. He entered Tufts College Medical School in 1909 and well earned the citation *Summa cum Laude* given with his degree in 1913. While in medical school he was appointed student laboratory assistant under Drs. Timothy Leary, in pathology, and Alfred Balch, in medical chemistry. Upon completion of internship at the Carney Hospital, New York Lying-in Hospital and Free Hospital for Women, he was appointed junior surgeon in the Department of Gynecology at the Carney Hospital. When engaged only a short time in practice he recognized a greater responsibility, gave up practice, applying for a commission in the Medical Corps in World War I. After release from service he opened his office at 270 Commonwealth Avenue, Boston, where he remained in active practice until six days before his death.

Following the death of his former chief, Frederick W. Johnson, he indeed became the active chief. He organized the Department of Obstetrics at the Carney Hospital. He became consultant to 13 hospitals throughout New England. The trustees named him full professor and head of the Department of Gynecology at Tufts College Medical School, and he became professor emeritus within the past year. He accomplished in considerable degree what he hoped for in the postgraduate training of physicians for work in gynecology. Several of those who served under him are now in charge of departments in medical schools or hospitals. One hundred and twenty-six articles written by him in English and others in French were published, the first in the December 20, 1917, issue of the *Boston Medical and Surgical Journal*, and the last in *Surgery, Gynecology and Obstetrics* for March, 1953. Outstanding in his writings are clear accounts of procedures he developed in the cure of vesicovaginal, ureterovesicovaginal and enterovesicovaginal fistulas. Important too and instructive were expressions of his thoughts on complete tears of the perineum with incontinence. Mortality after cesarean section under him was reduced to 0.9 per cent at the Carney Hospital, and this figure includes repeat procedures, 5 in number, on at least 2 patients now living.

An honorary degree of doctor of science was bestowed on him at Tufts and later by Laval University Faculty of Medicine. He had been a member of and active worker in important national, sectional and state medical societies and a former member of the Council of the Massachusetts Medical Society. To his devoted wife, Florence (Alles), he attributed much of his accomplishment. A sister and four brothers survive him. He lived a full and useful life.

Much that he taught and practiced in obstetrics and particularly gynecology will continue to guide workers in these fields for the betterment of many patients.

W. E. B.

APPLICANTS FOR FELLOWSHIP

Barnstable

Mandelstam, Abe W., Cape Cod Hospital, Hyannis.
Dalhousie University, Halifax, N. S., 1937.

Bristol South

Downey, William Stephen, Jr., 337 Union Street, New Bedford.
Harvard Medical School, 1949.

Hampden

McCarthy, Joseph Clement, 26 Mulberry Street, Springfield.
Georgetown University School of Medicine, 1943.
Transfer from District of Columbia.

Turner, Howard G., Jr., 289 State Street, Springfield.
Columbia University College of Physicians and Surgeons, 1943.
Transfer from Connecticut State Medical Society.

Walence, Edmond Michael, 16 Montrose Street, Springfield.
Georgetown University School of Medicine, 1951.

MIDDLESEX NORTH

RODGER, ROBERT COURT, 55 Belrose Avenue, Lowell.
Harvard Medical School, 1946.

SUFFOLK

FERRUCCI, JAMES C., 91 Crest Avenue, Chelsea.
Tufts College Medical School, 1948.

HAYMAN, JOSEPH M., JR., 136 Harrison Avenue, Boston.
University of Pennsylvania Medical School, 1921.

HORENSTEIN, SIMON, 818 Harrison Avenue, Boston.
University of Illinois Medical School, 1948.

BOOK REVIEWS

New Outlook on Mental Diseases. By F. A. Pickworth, M.B., B.Sc. 4°, cloth, 296 pp., with 41 illustrations. Baltimore: Williams and Wilkins, 1952. $12.00.

This comprehensive book approaches the problems of mental illness in a conservative and systematic way. Contrary to the title, the approach is not new, representing rather a return from certain accepted attitudes toward mind and mental disorders back to the ancient somatic foundation, but the book arrives where everyone finds himself today — that is, with well defined nerves and mental conditions requiring treatment. Since the primarily psychologic, "functional" and psychoanalytic-sociologic features of mental illness have been well documented in recent years, Pickworth's review of the whole problem is valuable as an outlook that is primarily that of the pathologist and research specialist. The chapter on cerebral blood supply gives prominent mention to Drs. Stanley Cobb, W. G. Lennox and J. H. Talbott. The sections dealing with neurology refer several times to the important scientific contributions of Dr. Derek Denny-Brown, and other experts well known in New England and throughout the United States are accorded the position of authorities in the splendid reference section, which includes 616 items. Chapter 10, "The Nature of Mind," is not original, but it is comprehensive and systematic, and well might have been made into a small monograph worth reading for the many ideas (some nearly forgotten) that it revives in a modern setting.

MERRILL MOORE, M.D.

The Mechanisms of Disease: A study of the autonomic nervous system, the endocrine system and the electrolytes in their relationship to clinical medicine. By Joseph Stambul, M.D. With a foreword by George M. Piersol, B.S., M.D. 8°, cloth, 746 pp. New York: Froben Press, Incorporated, 1952. $15.00.

It is Dr. Stambul's thesis that the mechanisms of disease must be sought at the level of individual cells and that they depend on the functional integrity of the cellular membranes. In health, metabolites pass in and out of the cell in proper amounts because a correct balance of cellular permeability is maintained by three controls: the autonomic nerves, hormones and electrolytes. In disease, on the contrary, these controls are deranged, membrane permeability is increased, and "vital chemical constituents" are lost from the cytoplasm. Under the influence of adrenergic impulses, for example, the permeability of hepatic cells is said to be increased with release of "glucose, amino acids, phospholipids, urea, creatine, fat soluble vitamins and blood serum proteins" into the circulation. Opposite effects are credited to parasympathetic activity.

To support his contentions, the author presents a massed battery of 1800 references. The very size of the bibliography, however, imposes its own limitations: on many pages the text deteriorates into a tedious and sometimes repetitious listing of one brief abstract after another, and the task of reading and abstracting so many references apparently prevented the author from considering much material published in the past decade. As a result, the reader may be presented with a highly specific hypothesis concerning, for example, hepatic secretory function, but the bases of the hypothesis are beliefs that since have been discarded.

Dr. Stambul's purpose — to focus attention on cellular mechanisms — certainly must have a great deal of merit. Whether his speculations will eventually prove correct cannot be decided on the basis of present knowledge. The validity of the reasoning, however, may be challenged. In his enthusiasm to carry his point, the author appears to extract only favorable material from his references; alternative interpretations and contrary evidence are not considered. Because of the emphasis of membrane permeability, moreover, important problems are glossed over: the author makes no distinction whether the "excited" liver cell releases glucose or glycogen into the blood. Finally, clinical conditions are molded with great facility to fit the theory. With decreased hepatic stores of a substance, for example, the theory calls for elevated blood levels. That this is not true of glycogen glucose in Addison's disease or vitamin A in hepatitis is either ignored or covered by the incorrect implication that blood levels of vitamin A are increased in liver disease.

The organization of the book suffers from repetitiousness and the inclusion of extraneous material. Its appeal will be chiefly for the man working in academic medical fields, to whom the ideas will prove stimulating if unconvincing and the extensive bibliography will widen his horizon. Although the chapters contain a brief section entitled "Summary and Practical Considerations," the considerations are limited and practical to the extent that "section of the vagus nerves to the liver" is suggested as the treatment for "severe and persistent cases of hypoglycemia" not caused by hyperinsulinism.

FRANZ J. INGELFINGER, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Frazer's Manual of Embryology: The development of the human body. By J. S. Baxter, M. A., M.Sc., M.D., F.R.C.S.I., professor of anatomy, University College, Cardiff. Third edition. 8°, cloth, 488 pp., with 288 illustrations. London: Baillière, Tindall and Cox, 1953. $8.00.

The text of this manual, first published in 1931, is divided into two parts on the early and general development, and on the development of separate organs and regions. Dr. Baxter has permitted the second part to remain much as the late Professor Frazer wrote it. The first section has been practically rewritten to bring the subject up to date, and a number of illustrations have been added. The publishing is excellent.

Rose and Carless' Manual of Surgery for Students and Practitioners. By Sir Cecil Wakeley, Bt., K.B.E., C.B., LL.D., M.Ch., D.Sc., F.R.C.S., F.R.S.E., F.R.S.A., fellow of King's College, London, president of the Royal College of Surgeons of England, senior surgeon, King's College Hospital, director of surgical studies and lecturer in surgery, King's College Hospital Medical School, surgeon, Belgrave Hospital for Children and Royal Masonic Hospital, consulting surgeon to the Royal Navy, and examiner in surgery to the University of Cambridge. Assisted by 18 contributors. Eighteenth edition. 8°, cloth, 1471 pp., with 1011 illustrations. Baltimore: Williams and Wilkins, 1952. $12.00.

This British book has had an unusual printing history. First published in 1898, it has gone through 46 printings in England and America, and has been translated into Arabic, Chinese (three editions) and Hungarian; the editor, Sir Cecil Wakeley, is an eminent British surgeon. It is the joint work of 18 specialists in their particular fields. It is a practical book and does not refer to any literature. There is a good index. The printing, which was done in Great Britain, is excellent.

New Outlook on Mental Diseases. By F. A. Pickworth, M.B., B.Sc., consultant pathologist, Group 6 Hospitals, Birmingham, England. 4°, cloth, 296 pp., with 41 illustrations. Baltimore: Williams and Wilkins, 1952. $12.00.

Psychology of Physical Illness: Psychiatry applied to medicine, surgery and the specialties. Edited by Leopold Bellak, M.D., clinical assistant professor of psychiatry, New York Medical College, Flower and Fifth Avenue Hospitals, New York City. 8°, cloth, 243 pp. New York: Grune and Stratton, 1952. $5.50.

Human Blood Coagulation and its Disorders. By Rosemary Biggs, B. Sc. (Lond.), Ph.D. (Toronto), M.D. (Lond.), graduate assistant, Department of Pathology, Radcliffe Infirmary, Oxford; and R. G. Macfarlane, M.A. (Oxon.), M.D.(Lond.), clinical pathologist, Radcliffe Infirmary, Oxford, and Radcliffe Lecturer in Haematology, University of Oxford. 8°, cloth, 406 pp., with 54 illustrations and 36 tables. Springfield, Illinois: Charles C Thomas, 1953. $8.00.

This monograph thoroughly covers human blood coagulation in all its aspects. The text is divided into two parts: general and physiologic; and disorders. The pertinent literature is surveyed, and there is a bibliography of 30 pages. The printing was done in Great Britain, and the publishing is excellent. The book should be in all medical libraries as a reference work.

The Alcoholism Research Foundation: Annual report for 1952. 4°, paper, 46 pp., with tables. Toronto: Alcoholism Research Foundation, 1953.

Urethrography in the Male with a Highly Viscous, Water-Soluble Contrast Medium, Umbradil-Viscous U. By Olallo Morales and Ragnar Romanus. (Supplementum 95, *Acta Radiologica.*) 91 pages. Sw. Kr. 20:- 8°, paper. Stockholm: Acta Radiologica, 1952.

The Importance of Adequate Stimulation for the Chemical Composition of Retinal Ganglion Cells during Early Post-Natal Development. By Sven Olof Brattgard. (Supplementum 96, *Acta Radiologica.*) 80 pages. Sw. Kr. 20:- 8°, paper. Stockholm: Acta Radiologica, 1952.

Therapeutics in Internal Medicine. By eighty-four authorities. Edited by Franklin A. Kyser, M.D., assistant professor of medicine, Northwestern University Medical School, and attending physician, Evanston Hospital, Evanston, Illinois. Second edition. 8°, cloth, 830 pp. New York: Paul B. Hoeber, Incorporated, 1953. $15.00.

This second edition of a composite work on therapeutics has been thoroughly revised to bring the treatment of medical diseases up to date; 12 new sections and 17 new contributors have been included in this edition. The whole field of medicine has been covered, including diseases of the nervous system and of the skin. There is an extensive index, and the book is well published.

Rehabilitation of the Physically Handicapped. By Henry H. Kessler. Revised edition. 8°, cloth, 275 pp. New York: Columbia University Press, 1953. $4.00.

Dr. Kessler has revised this edition of his book on rehabilitation first published in 1947. The text is divided into four parts: the problems of the physically handicapped; principles; practice of rehabilitation; and a national program. An appendix lists the major centers and agencies for the handicapped. There is a good index, and the book is well published. It should be in all collections on the subject.

Diuretic Therapy: The pharmacology of diuretic agents and the clinical management of the edematous patient. By Alfred Vogl, M.D., assistant professor of clinical medicine, New York University College of Medicine, associate visiting physician, Third Medical Division, Bellevue Hospital, and associate visiting physician, Medical Division, Metropolitan Hospital, New York City. 8°, cloth, 248 pp., with illustrations. Baltimore: Williams and Wilkins, 1953. $5.00.

Dr. Vogl discusses in detail edema, the pharmacology of the diuretic drugs and their action and effectiveness, antidiuretic agents and the practice of diuretic therapy. The important literature is evaluated; there is a bibliography of 725 items. The book should be in all medical libraries.

Tumors of Bone: A roentgenographic atlas. By Bradley L. Coley, M.D., attending surgeon, Bone Service, Memorial Center for Cancer and Allied Diseases, and associate professor of clinical surgery, Cornell University Medical College; and Norman L. Higinbotham, M.D., C.M., associate attending surgeon, Bone Service, Memorial Center for Cancer and Allied Diseases, and assistant professor of clinical surgery, Cornell University Medical College. 4°, cloth, 16 pp., with 172 illustrations. New York: Paul B. Hoeber, Incorporated, 1953. $10.00. (*Annals of Roentgenology*, Volume 21.)

This new volume in a special series of atlases describes the various types of tumors afflicting bone. There is a chapter on non-neoplastic conditions of bone simulating bone tumors. The atlas should be in all collections on orthopedics and roentgenology.

Clinical Orthopaedics. Number One. Anthony F. DePalma, editor-in-chief. 4°, cloth, 242 pp., with 149 illustrations. Philadelphia: J. B. Lippincott Company, 1953. On sustaining basis, $5.00 each; single number, $6.00 each.

This first number of a projected serial contains articles by 29 contributors. The material is divided into two parts on children's and general orthopedics on a variety of topics. There is a good index, and the publishing is excellent. The volume and its continuations should be in all medical and orthopedic collections.

Human Neuroanatomy. By Oliver S. Strong; and Adolph Elwyn, associate professor of neuroanatomy, Columbia University, College of Physicians and Surgeons. Third edition. 4°, cloth, 481 pp., with 357 illustrations. Baltimore: Williams and Wilkins, 1953. $7.50.

This special book, the first edition of which was published in 1943, has now gone through 3 editions and 4 reprintings. The text has been thoroughly revised and some sections rewritten, especially on the nerve cell and fiber, including the processes of degeneration and regeneration, the cerebellum, the thalamic nuclei and their connections, the subthalamus and the reticular system of the brain stem. Thirty-four illustrations have been added. There is a bibliography of 15 pages and an extensive index. The book should be in all collections on neurology and anatomy.

Gout and Gouty Arthritis. By John H. Talbott, M.D., Professor of Medicine, University of Buffalo School of Medicine, and physician-in-chief, Buffalo General Hospital, Buffalo. 8°, cloth, 92 pp., with 32 illustrations. New York: Grune and Stratton, 1953. $4.00. (*Modern Medical Monographs* No. 7.)

Chronic Pulmonary Emphysema: Physiopathology and treatment. By Maurice S. Segal, M.D., clinical professor of medicine, Tufts College Medical School, and director, Department of Inhalational Therapy, Boston City Hospital; and M. J. Dulfano, M.D., research fellow in medicine, Tufts College Medical School, and resident, Department of Inhalational Therapy, Boston City Hospital. 8°, cloth, 180 pp., with 31 illustrations and 9 tables. New York: Grune and Stratton, 1953. $5.50. (*Modern Medical Monographs* No. 8.)

Clinical Cardiology. Edited by Franklin C. Massey, M.D., assistant professor of medicine, Hahnemann Medical College. 8°, cloth, 1100 pp., with illustrations. Baltimore: Williams and Wilkins, 1953. $13.50.

Fundamentals of Clinical Orthopedics. By Peter A. Casagrande, M.D., member, Orthopedic Department, Buffalo Children's Hospital and University of Buffalo School of Medicine, and attending orthopedist, Chronic Disease Research Institute, University of Buffalo and Veterans Administration Hospital, Buffalo; and Harold M. Frost, Jr., M.D., member, Orthopedic Department, Buffalo General Hospital and University of Buffalo School of Medicine. With forewords by Joseph S. Barr, M.D., and Frank N. Potts, M.D. 4°, cloth, 582 pp, with 390 illustrations. New York: Grune and Stratton, 1953. $18.50.

Sexual Harmony in Marriage. By Oliver M. Butterfield, Ph.D., professor of family life education, Mount San Antonio College. With an introduction by Nadina Kavinoky, M.D., member, Department of Gynecology, College of Medical Evangelists, and School of Nursing, Methodist Hospital. 12°, cloth, 96 pp., with 3 illustrations. New York: Emerson Books, Incorporated, 1953. $1.50.

Bioassay of Anterior Pituitary and Adrenocortical Hormones. G. E. W. Wolstenholme, O.B.E.,M.A., M.B., B.Ch., general editor for the Ciba Foundation. Assisted by Margaret P. Cameron, M. A., A.B.L.S. 8°, cloth, 228 pp., with 53 illustrations. Boston: Little, Brown and Company, 1953. $6.00. (*Ciba Foundation Colloquia on Endocrinology*, Vol. V.)

This volume of an important series was printed in Great Britain. The series as projected will comprise 7 volumes. The set should be in all collections on endocrinology.

Dictionary of Psychiatry and Psychology: An illustrated condensed encyclopedia of psychiatry, neurology and psychology. By William H. Kupper, M.D. With a foreword by Douglas M. Kelly, M.D., professor of criminology, University of California. 8°, cloth, 194 pp. Paterson 3, New Jersey: Colt Press, 1953.

This new semi-dictionary presents a number of interesting features, such as a list of state hospitals for the insane, arranged by states, a table of admissions to hospitals for the insane and a list of psychiatric and psychologic journals.

NONCLINICAL NOTES

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

The officers of the New England Society of Anesthesiologists for the coming year are as follows: President, Dr. Stevens J. Martin, Hartford, Connecticut; Vice-President, Dr. Elihu Saklad, Providence, Rhode Island; Secretary-Treasurer, Dr. Francis J. Audin, Boston, Massachusetts.

NOTICES

NEW YORK SOCIETY FOR CIRCULATORY DISEASES

The tenth regular meeting of the New York Society for Circulatory Diseases will be held in Room 440 in the New York Academy of Medicine, 2 East 103 Street, New York City, on Tuesday, December 8, at 8:30 p.m. The topic of the meeting will be "Treatment of Acute Cardiac Emergencies in Myocardial Infarction." The speakers will be Dr. Maurice L. Tainter, director, Sterling-Winthrop Research Institute, Rensselaer, New York, and Dr. Herbert J. Kayden, clinical instructor in medicine, New York University College of Medicine, assistant visiting physician, Goldwater Memorial Hospital, and assistant attending physician, University Hospital. Dr. Simon Dack will preside. Further information may be obtained from the secretary, Dr. Gabriel F. Greco, 114-08 Linden Boulevard, Ozone Park 16, New York.

UNIVERSITY OF BUFFALO SCIENTIFIC SYMPOSIUMS

Scientific symposiums will be held at the University of Buffalo in connection with dedication exercises for Samuel P. Capen Hall, the new building for the medical and dental schools, December 11 and 12. Participants in the program will include Dr. Charles H. Best, Dr. Robin R. A. Coombs, Dr. Stanley E. Dorst and Dr. Maynard K. Hine. Dr. Samuel P. Capen, chancellor emeritus of the University of Buffalo, will be the guest of honor.

SOCIETY MEETINGS AND CONFERENCES

NOVEMBER 20–DECEMBER 18. Boston Lying-in Hospital Journal Club. Page 672, issue of October 15.

NOVEMBER 23–DECEMBER 15. Boston City Hospital House Officers' Association Lectures. Page 789, issue of November 5.

NOVEMBER 25. Consultation Clinic for Crippled Children. Page 713, issue of October 22.

NOVEMBER 28. Phi Delta Epsilon Fraternity Dance. Page 828, issue of November 12.

NOVEMBER 28 and 29. International College of Surgeons. Regional Meeting. Page 828, issue of November 12.

DECEMBER 2. Course in Child Psychiatry (Pediatric Neuropsychiatry). Page 428, issue of September 3.

DECEMBER 2. New England Conference on Allergy and Related Subjects. Page 828, issue of November 12.

DECEMBER 6. American Academy of Dental Medicine. Page 170, issue of July 23.

DECEMBER 8. New York Society for Circulatory Diseases. Notice above.

DECEMBER 11 and 12. New York and Brooklyn Regional Committee on Trauma, American College of Surgeons. Page 828, issue of November 12.

DECEMBER 11 and 12. University of Buffalo Scientific Symposiums. Notice above.

DECEMBER 21. Hartford Medical Society Program. Page 260, issue of August 6.

DECEMBER 28. American Association for the Advancement of Science. Page 828, issue of November 12.

JANUARY 6, MARCH 3 and APRIL 21, 1954. Massachusetts Society for Research in Psychiatry. Page 750, issue of October 29.

JANUARY 22, 23, 29 and 30. International College of Surgeons. Regional Meeting. Page 828, issue of November 12.

FEBRUARY 2–4. Examination for Public Health Service Medical Officers. Page 750, issue of October 29.

FEBRUARY 15–20. Pan-American Academy of General Practice. Page 790, issue of November 5.

MAY 31–JUNE 3. American Urological Association. Page xvii, issue of July 23.

JULY 22 and 23. International College of Surgeons. Regional Meeting. Page 828, issue of November 12.

SEPTEMBER 7–10. Nineteenth Annual Congress of the United States and Canadian Sections of the International College of Surgeons. Page 828, issue of November 12.

SEPTEMBER 12–15. Second International Congress of Cardiology. Page 44, issue of July 2.

SEPTEMBER 16–18. American Heart Association. Annual Scientific Sessions. Page 44, issue of July 2.

DISTRICT MEDICAL SOCIETY

MIDDLESEX EAST

JANUARY 20. (Combined with the Auxiliary.)

MARCH 24.

MAY 11. Annual Meeting. (Harlow Dinner.)

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, NOVEMBER 26

THURSDAY, NOVEMBER 26. Holiday.

FRIDAY, NOVEMBER 27

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit. 57 East Concord Street.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

11:00 a.m.–1:00 p.m. Medical Grand Rounds. Stearns Auditorium, New England Center Hospital.

*12:30–1:30 p.m. Shock. Dr. D. Branch. Ward B Classroom, Cambridge City Hospital.

*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.

*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.

2:00–3:30 p.m. Hematology Clinic. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

4:00–6:00 p.m. X-ray Conference. Dr. Merrill Sosman. Stearns Auditorium, New England Center Hospital.

*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

SATURDAY, NOVEMBER 28

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.

*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.

9:00–10:30 a.m. Surgical Grand Rounds. Stearns Auditorium, New England Center Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

11:00 a.m.–12:00 m. Blood Clinic. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, NOVEMBER 30

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Foot Problems. New England Deaconess Hospital.

8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff, Cheever Amphitheater, Dowling Building, Boston City Hospital.

(*Notices concluded on page xxi*)